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FILE 'STNGUIDE' ENTERED AT 10:17:07 ON 17 FEB 2004

FILE 'REGISTRY' ENTERED AT 10:19:00 ON 17 FEB 2004
E VENLAFAXINE/CN
L1 1 S E3

FILE 'CAPLUS' ENTERED AT 10:19:22 ON 17 FEB 2004
L2 1 S L1/PUR
L3 625 S L1
L4 224816 S WHITE
L5 3 S L3 AND L4
L6 903870 S PURI?
L7 0 S L3 (P) L6
L8 13 S L3 AND L6

=> d bib abs kwic 1-13

L8 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:221518 CAPLUS
DN 138:215345
TI Combination of an adenosine A2A receptor antagonist and an antidepressant or anxiolytic
IN Greenlee, William J.; Hunter, John
PA Schering Corporation, USA
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003022283	A1	20030320	WO 2002-US28865	20020911
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2003139395	A1	20030724	US 2002-241120	20020911
PRAI	US 2001-318696P	P	20010913		

AB This invention relates to a method of treating depression and anxiety-related disorders comprising administering to a mammal in need of such treatment an effective amount of a combination of an adenosine A2A antagonist and an antidepressant or an anxiolytic; another aspect of the invention is a pharmaceutical composition comprising a therapeutically effective amount of a combination of an adenosine A2A antagonist and an antidepressant or anxiolytic in a pharmaceutically acceptable carrier.
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT **Purinoceptor** antagonists
(A2; combination of an adenosine A2A receptor antagonist and an antidepressant or anxiolytic)
IT 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine
57-53-4, Meprobamate 58-25-3, Chlordiazepoxide 72-69-5, Nortriptyline

439-14-5, Diazepam 846-49-1, Lorazepam 1622-61-3, Clonazepam
1668-19-5, Doxepin 28981-97-7, Alprazolam 34911-55-2, Bupropion
36505-84-7, Buspirone 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine
59729-33-8, Citalopram 61869-08-7, Paroxetine 71620-89-8, Reboxetine
79617-96-2, Sertraline 83366-66-9, Nefazodone 85650-52-8, Mirtazepine
92623-85-3, Milnacipran **93413-69-5**, Venlafaxine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination of an adenosine A2A receptor antagonist and an antidepressant or anxiolytic)

L8 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:202410 CAPLUS
DN 138:226705
TI Novel pharmaceuticals comprising drug conjugates with polypeptide carriers
IN Picariello, Thomas
PA New River Pharmaceuticals Inc., USA
SO PCT Int. Appl., 2059 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003020200	A2	20030313	WO 2001-US43117	20011116
	WO 2003020200	A3	20030912		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1357928	A2	20031105	EP 2001-273387	20011116
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRAI	US 2000-248600P	P	20001116
	US 2000-248601P	P	20001116
	US 2000-248603P	P	20001116
	US 2000-248604P	P	20001116
	US 2000-248606P	P	20001116
	US 2000-248607P	P	20001116
	US 2000-248608P	P	20001116
	US 2000-248609P	P	20001116
	US 2000-248611P	P	20001116
	US 2000-248689P	P	20001116
	US 2000-248691P	P	20001116
	US 2000-248692P	P	20001116
	US 2000-248693P	P	20001116
	US 2000-248694P	P	20001116
	US 2000-248695P	P	20001116
	US 2000-248696P	P	20001116
	US 2000-248697P	P	20001116
	US 2000-248698P	P	20001116
	US 2000-248701P	P	20001116
	US 2000-248702P	P	20001116
	US 2000-248703P	P	20001116
	US 2000-248704P	P	20001116
	US 2000-248705P	P	20001116
	US 2000-248706P	P	20001116

US 2000-248707P	P	20001116
US 2000-248708P	P	20001116
US 2000-248709P	P	20001116
US 2000-248710P	P	20001116
US 2000-248711P	P	20001116
US 2000-248712P	P	20001116
US 2001-248664P	P	20011116
US 2001-248665P	P	20011116
US 2001-248666P	P	20011116
US 2001-248667P	P	20011116
US 2001-248668P	P	20011116
US 2001-248669P	P	20011116
US 2001-248671P	P	20011116
US 2001-248672P	P	20011116
US 2001-248673P	P	20011116
US 2001-248674P	P	20011116
US 2001-248675P	P	20011116
US 2001-248676P	P	20011116
US 2001-248677P	P	20011116
US 2001-248678P	P	20011116
US 2001-248679P	P	20011116
US 2001-248680P	P	20011116
US 2001-248681P	P	20011116
US 2001-248682P	P	20011116
US 2001-248683P	P	20011116
US 2001-248684P	P	20011116
US 2001-248765P	P	20011116
US 2001-248766P	P	20011116
US 2001-248767P	P	20011116
US 2001-248773P	P	20011116
US 2001-248774P	P	20011116
US 2001-248775P	P	20011116
US 2001-248778P	P	20011116
US 2001-248780P	P	20011116
US 2001-248781P	P	20011116
US 2001-248783P	P	20011116
US 2001-248784P	P	20011116
US 2001-248785P	P	20011116
US 2001-248786P	P	20011116
US 2001-248787P	P	20011116
US 2001-248790P	P	20011116
US 2001-248791P	P	20011116
US 2001-248792P	P	20011116
US 2001-248793P	P	20011116
US 2001-248833P	P	20011116
US 2001-248848P	P	20011116
US 2001-248849P	P	20011116
WO 2001-US43117	W	20011116

AB A pharmaceutical composition comprising a polypeptide and an active agent attached to said polypeptide is disclosed.

IT **Purinoceptor** antagonists
(A1, polypeptide conjugates; novel pharmaceuticals comprising drug conjugates with polypeptide carriers)

IT 50-06-6D, Phenobarbital, polypeptide conjugates 50-35-1D, Thalidomide, polypeptide conjugates 50-81-7D, Vitamin c, polypeptide conjugates 51-21-8D, Fluorouracil, polypeptide conjugates 51-48-9D, Levothyroxine, polypeptide conjugates 52-01-7D, Spironolactone, polypeptide conjugates 52-24-4D, Thiotepa, polypeptide conjugates 52-53-9D, Verapamil, polypeptide conjugates 53-03-2D, Prednisone, polypeptide conjugates 55-63-0D, Nitroglycerin, polypeptide conjugates 57-27-2D, Morphine, polypeptide conjugates 57-41-0D, Phenytoin, polypeptide conjugates 57-63-6D, Ethinyl estradiol, polypeptide conjugates 58-55-9D,

Theophylline, polypeptide conjugates 58-93-5D, Hydrochlorothiazide, polypeptide conjugates 60-54-8D, Tetracycline, polypeptide conjugates 60-87-7D, Promethazine, polypeptide conjugates 67-20-9D, Nitrofurantoin, polypeptide conjugates 68-19-9D, Vitamin b12, polypeptide conjugates 68-22-4D, Norethindrone, polypeptide conjugates 71-58-9D, Medroxyprogesterone acetate, polypeptide conjugates 72-69-5D, Nortriptyline, polypeptide conjugates 74-79-3D, Arginine, polypeptide conjugates 76-42-6D, Oxycodone, polypeptide conjugates 76-57-3D, Codeine, polypeptide conjugates 81-81-2D, Warfarin, polypeptide conjugates 83-43-2D, Methylprednisolone, polypeptide conjugates 84-02-6D, Prochlorperazine maleate, polypeptide conjugates 87-08-1D, Penicillin v, polypeptide conjugates 89-57-6D, Mesalamine, polypeptide conjugates 90-82-4D, Pseudoephedrine, polypeptide conjugates 99-66-1D, Valproic acid, polypeptide conjugates 103-90-2D, Acetaminophen, polypeptide conjugates 113-45-1D, Methylphenidate, polypeptide conjugates 114-07-8D, Erythromycin, polypeptide conjugates 125-33-7D, Primidone, polypeptide conjugates 128-13-2D, Ursodiol, polypeptide conjugates 396-01-0D, Triamterene, polypeptide conjugates 443-48-1D, Metronidazole, polypeptide conjugates 469-62-5D, Propoxyphene, polypeptide conjugates 525-66-6D, Propranolol, polypeptide conjugates 541-15-1D, Levocarnitine, polypeptide conjugates 554-13-2D, Lithium carbonate, polypeptide conjugates 595-33-5D, Megestrol acetate, polypeptide conjugates 604-75-1D, Oxazepam, polypeptide conjugates 657-24-9D, Metformin, polypeptide conjugates 846-49-1D, Lorazepam, polypeptide conjugates 846-50-4D, Temazepam, polypeptide conjugates 1247-42-3D, Methylprednisone, polypeptide conjugates 1404-90-6D, Vancomycin, polypeptide conjugates 1508-65-2D, Oxybutynin chloride, polypeptide conjugates 1665-48-1D, Metaxalone, polypeptide conjugates 1744-22-5D, Riluzole, polypeptide conjugates 2078-54-8D, Propofol, polypeptide conjugates 2152-34-3D, Pemoline, polypeptide conjugates 3056-17-5D, Stavudine, polypeptide conjugates 3930-20-9D, Sotalol, polypeptide conjugates 4682-36-4D, Orphenadrine citrate, polypeptide conjugates 6493-05-6D, Pentoxifylline, polypeptide conjugates 6893-02-3D, TriIodothyronine, polypeptide conjugates 9002-69-1D, Relaxin, polypeptide conjugates 9004-10-8D, Insulin, polypeptide conjugates 9005-49-6D, Heparin, polypeptide conjugates 9014-42-0D, Thrombopoietin, polypeptide conjugates 9039-53-6D, Urokinase, polypeptide conjugates 10118-90-8D, Minocycline, polypeptide conjugates 10540-29-1D, Tamoxifen, polypeptide conjugates 11056-06-7D, Bleomycin, polypeptide conjugates 13392-28-4D, Rimantadine, polypeptide conjugates 14611-51-9D, Selegiline, polypeptide conjugates 17560-51-9D, Metolazone, polypeptide conjugates 19767-45-4D, Mesna, polypeptide conjugates 19794-93-5D, Trazodone, polypeptide conjugates 21256-18-8D, Oxaprozin, polypeptide conjugates 21829-25-4D, Nifedipine, polypeptide conjugates 22204-53-1D, Naproxen, polypeptide conjugates 23031-32-5D, Terbutaline sulfate, polypeptide conjugates 27203-92-5D, Tramadol, polypeptide conjugates 27314-97-2D, Tirapazamine, polypeptide conjugates 30516-87-1D, Zidovudine, polypeptide conjugates 31441-78-8D, Mercaptopurine, polypeptide conjugates 33069-62-4D, Paclitaxel, polypeptide conjugates 36791-04-5D, Ribavirin, polypeptide conjugates 37300-21-3D, Pentosan polysulfate, polypeptide conjugates 40391-99-9D, polypeptide conjugates 42200-33-9D, Nadolol, polypeptide conjugates 42924-53-8D, Nabumetone, polypeptide conjugates 49842-07-1D, Tobramycin sulfate, polypeptide conjugates 50700-72-6D, Vecuronium, polypeptide conjugates 50851-57-5D, polypeptide conjugates 51321-79-0D, Sparfosic acid, polypeptide conjugates 51322-75-9D, Tizanidine, polypeptide conjugates 51384-51-1D, Metoprolol, polypeptide conjugates 52232-67-4D, Teriparatide, polypeptide conjugates 52757-95-6D, Sevelamer, polypeptide conjugates 53179-11-6D, Loperamide, polypeptide conjugates 53230-10-7D, Mefloquine, polypeptide conjugates 54024-22-5D, Desogestrel, polypeptide conjugates 54182-58-0D, Sucralfate, polypeptide conjugates 55142-85-3D, Ticlopidine, polypeptide

conjugates 56211-40-6D, Torsemide, polypeptide conjugates 59122-46-2D, Misoprostol, polypeptide conjugates 61477-96-1D, Piperacillin, polypeptide conjugates 61512-21-8D, Thymosin, polypeptide conjugates 61869-08-7D, Paroxetine, polypeptide conjugates 63590-64-7D, Terazosin, polypeptide conjugates 63675-72-9D, Nisoldipine, polypeptide conjugates 65271-80-9D, Mitoxantrone, polypeptide conjugates 65807-02-5D, Goserelin, polypeptide conjugates 66085-59-4D, Nimodipine, polypeptide conjugates 66104-22-1D, Pergolide, polypeptide conjugates 66357-35-5D, Ranitidine, polypeptide conjugates 68562-41-4D, Mecasermin, polypeptide conjugates 68693-11-8D, Modafinil, polypeptide conjugates 70458-96-7D, Norfloxacin, polypeptide conjugates 73590-58-6D, Omeprazole, polypeptide conjugates 74381-53-6D, Leuprolide acetate, polypeptide conjugates 75330-75-5D, Lovastatin, polypeptide conjugates 75970-99-9D, Norastemizole, polypeptide conjugates 76470-66-1D, Loracarbef, polypeptide conjugates 76547-98-3D, Lisinopril, polypeptide conjugates 76963-41-2D, Nizatidine, polypeptide conjugates 79517-01-4D, Octreotide acetate, polypeptide conjugates 79617-96-2D, Sertraline, polypeptide conjugates 79794-75-5D, Loratidine, polypeptide conjugates 79902-63-9D, Simvastatin, polypeptide conjugates 81093-37-0D, Pravastatin, polypeptide conjugates 81627-83-0D, Mcsf, polypeptide conjugates 82419-36-1D, Ofloxacin, polypeptide conjugates 82626-48-0D, Zolpidem, polypeptide conjugates 82657-92-9D, Prourokinase, polypeptide conjugates 83015-26-3D, Tomoxetine, polypeptide conjugates 83200-96-8D, Carbapenem, polypeptide conjugates 83366-66-9D, Nefazodone, polypeptide conjugates 83799-24-0D, Fexofenadine, polypeptide conjugates 84449-90-1D, Raloxifene, polypeptide conjugates 85441-61-8D, Quinapril, polypeptide conjugates 85650-52-8D, Mirtazapine, polypeptide conjugates 87333-19-5D, Ramipril, polypeptide conjugates 87679-37-6D, Trandolapril, polypeptide conjugates 90566-53-3D, Fluticasone, polypeptide conjugates 91161-71-6D, Terbinafine, polypeptide conjugates 91374-21-9D, Ropinirole, polypeptide conjugates 91421-42-0D, Rubitecan, polypeptide conjugates **93413-69-5D**, Venlafaxine, polypeptide conjugates 95635-55-5D, Ranolazine, polypeptide conjugates 96036-03-2D, Meropenem, polypeptide conjugates 96829-58-2D, Orlistat, polypeptide conjugates 97240-79-4D, Topiramate, polypeptide conjugates 97322-87-7D, Troglitazone, polypeptide conjugates 99614-02-5D, Ondansetron, polypeptide conjugates 100286-97-3D, Milrinone lactate, polypeptide conjugates 100986-85-4D, Levofloxacin, polypeptide conjugates 103475-41-8D, Tepoxalin, polypeptide conjugates 103628-46-2D, Sumatriptan, polypeptide conjugates 103775-10-6D, Moexipril, polypeptide conjugates 104632-26-0D, Pramipexole, polypeptide conjugates 106133-20-4D, Tamsulosin, polypeptide conjugates 106266-06-2D, Risperidone, polypeptide conjugates 106392-12-5D, Poloxamer 188, polypeptide conjugates 106650-56-0D, Sibutramine, polypeptide conjugates 107753-78-6D, Zafirlukast, polypeptide conjugates 109768-33-4D, Sulfx, polypeptide conjugates 111025-46-8D, Pioglitazone, polypeptide conjugates 111974-72-2D, Quetiapine fumarate, polypeptide conjugates 112733-06-9D, Zenarestat, polypeptide conjugates 114798-26-4D, Losartan, polypeptide conjugates 114977-28-5D, Docetaxel, polypeptide conjugates 115103-54-3D, Tiagabine, polypeptide conjugates 117976-89-3D, Rabeprazole, polypeptide conjugates 121032-29-9D, Nelarabine, polypeptide conjugates 121584-18-7D, Valspodar, polypeptide conjugates 121679-13-8D, Naratriptan, polypeptide conjugates 123774-72-1D, Sargramostim, polypeptide conjugates 123948-87-8D, Topotecan, polypeptide conjugates 124584-08-3D, Nesiritide, polypeptide conjugates 124832-26-4D, Valacyclovir, polypeptide conjugates 124937-51-5D, Tolterodine, polypeptide conjugates 125317-39-7D, Vinorelbine tartrate, polypeptide conjugates 127254-12-0D, Sitafloxacin, polypeptide conjugates 127779-20-8D, Saquinavir, polypeptide conjugates 128298-28-2D, Remacemide, polypeptide conjugates 128794-94-5D, Mycophenolate mofetil, polypeptide conjugates 129580-63-8D, Satraplatin, polypeptide conjugates 129618-40-2D, Nevirapine, polypeptide conjugates

130018-77-8D, Levocetirizine, polypeptide conjugates 131918-61-1D, Paricalcitol, polypeptide conjugates 132539-06-1D, Olanzapine, polypeptide conjugates 133737-32-3D, Pagoclone, polypeptide conjugates 133814-19-4D, Mivacurium, polypeptide conjugates 135062-02-1D, Repaglinide, polypeptide conjugates 135354-02-8D, Xaliproden, polypeptide conjugates 137234-62-9D, Voriconazole, polypeptide conjugates 137281-23-3D, Pemetrexed, polypeptide conjugates 137862-53-4D, Valsartan, polypeptide conjugates 138531-07-4D, Sinapultide, polypeptide conjugates 138660-96-5D, Sevirumab, polypeptide conjugates 139264-17-8D, Zolmitriptan, polypeptide conjugates 139639-23-9D, Tissue plasminogen activator, analogs, polypeptide conjugates 143558-00-3D, Rocuronium, polypeptide conjugates 144494-65-5D, Tirofiban, polypeptide conjugates 144980-29-0D, Repinotan, polypeptide conjugates 145202-66-0D, Rizatriptan benzoate, polypeptide conjugates 145375-43-5D, Mitiglinide, polypeptide conjugates 145941-26-0D, Oprelvekin, polypeptide conjugates 147059-75-4D, Trovafloxacin mesylate, polypeptide conjugates 148553-50-8D, Pregabalin, polypeptide conjugates 148883-56-1D, Tifacogin, polypeptide conjugates 151319-34-5D, Zaleplon, polypeptide conjugates 153168-05-9D, Pleconaril, polypeptide conjugates 154039-60-8D, Marimastat, polypeptide conjugates 155141-29-0D, Rosiglitazone maleate, polypeptide conjugates 155213-67-5D, Ritonavir, polypeptide conjugates 158966-92-8D, Montelukast, polypeptide conjugates 159989-65-8D, Nelfinavir mesylate, polypeptide conjugates 162011-90-7D, Rofecoxib, polypeptide conjugates 166089-32-3D, Lintuzumab, polypeptide conjugates 171228-49-2D, Posaconazole, polypeptide conjugates 171599-83-0D, Sildenafil citrate, polypeptide conjugates 180288-69-1D, Trastuzumab, polypeptide conjugates 181695-72-7D, Valdecoxib, polypeptide conjugates 188039-54-5D, Palivizumab, polypeptide conjugates 192329-42-3D, Prinomastat, polypeptide conjugates 193079-69-5D, Tabimorelin, polypeptide conjugates 201341-05-1D, Tenofovir disoproxil, polypeptide conjugates
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel pharmaceuticals comprising drug conjugates with polypeptide carriers)

L8 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:105228 CAPLUS
DN 138:349178
TI High-throughput confirmation of differential display PCR results using reverse Northern blotting
AU Dilks, Daniel W.; Ring, Robert H.; Khawaja, Xavier Z.; Novak, Thomas J.; Aston, Christopher
CS Neuroscience, CN-8000, Wyeth Research, Princeton, NJ, 08543-8000, USA
SO Journal of Neuroscience Methods (2003), 123(1), 47-54
CODEN: JNMEDT; ISSN: 0165-0270
PB Elsevier Science B.V.
DT Journal
LA English
AB Nylon filter arrays spotted with differential display PCR (DD-PCR) clones and hybridized with radiolabeled cRNA generated from the source RNA pool (reverse Northern blot) provide a high-throughput means to screen clones for artifacts. Reverse Northern blots also confirm differential gene expression in parallel and require modest quantities of the source RNA pool. We describe a strategy to screen multiple candidates from DD-PCR by high-throughput ligation and transformation, followed by reverse Northern blotting. **Purifn.** of re-amplified DD-PCR clones and fabrication of nylon arrays was facilitated by a batch-processing protocol using the widely available Biomek laboratory robot and Bioworks scripts (available from the authors). A strategy to screen out DD-PCR product artifacts of an inappropriate size was also employed. Using these approaches, we identified several mRNAs that are differentially expressed in response to venlafaxine, fluoxetine or desipramine antidepressant treatment in rat C6

glioma cell lines and are candidates for full length clone isolation using 5'-RACE. Such an approach provides a rapid means to eliminate the high percentage of false pos. clones from DD-PCR and enables independent confirmation of differential gene expression patterns generated by various exptl. conditions.

RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Nylon filter arrays spotted with differential display PCR (DD-PCR) clones and hybridized with radiolabeled cRNA generated from the source RNA pool (reverse Northern blot) provide a high-throughput means to screen clones for artifacts. Reverse Northern blots also confirm differential gene expression in parallel and require modest quantities of the source RNA pool. We describe a strategy to screen multiple candidates from DD-PCR by high-throughput ligation and transformation, followed by reverse Northern blotting. **Purifn**. of re-amplified DD-PCR clones and fabrication of nylon arrays was facilitated by a batch-processing protocol using the widely available Biomek laboratory robot and Bioworks scripts (available from the authors). A strategy to screen out DD-PCR product artifacts of an inappropriate size was also employed. Using these approaches, we identified several mRNAs that are differentially expressed in response to venlafaxine, fluoxetine or desipramine antidepressant treatment in rat C6 glioma cell lines and are candidates for full length clone isolation using 5'-RACE. Such an approach provides a rapid means to eliminate the high percentage of false pos. clones from DD-PCR and enables independent confirmation of differential gene expression patterns generated by various exptl. conditions.

IT 50-47-5, Desipramine 54910-89-3, Fluoxetine **93413-69-5**, Venlafaxine
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(differential mRNA expression in response to; high-throughput confirmation of differential display PCR results using reverse Northern blotting)

L8 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:5924 CAPLUS
DN 138:73016
TI Improved process for preparation of cyclohexanol derivatives, e.g., 1-[cyano(4-methoxyphenyl)methyl]cyclohexanol, a venlafaxine intermediate, from phenylacetonitriles and cyclohexanone, using non-organometallic bases.
IN Kim, Keun-sik; Kim, Kwang-il; Lee, Sung-woo; Park, Jin-soo; Chai, Ki-byung
PA Wyeth A Corporation of the State of Delaware, USA, USA
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

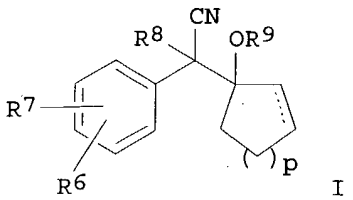
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003000652	A1	20030103	WO 2002-US19753	20020621

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

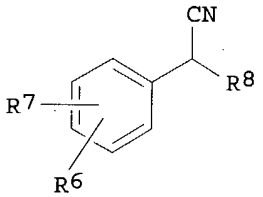
PRAI KR 2001-35889 A 20010622

10/290,245

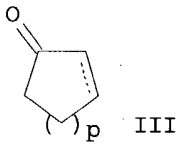
OS CASREACT 138:73016; MARPAT 138:73016
GI



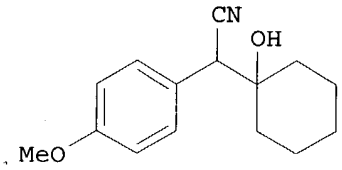
I



II



III



IV

AB An improved process for the preparation of cyanobenzylated cyclohexanol derivs. and analogs I is claimed [wherein: R6 and R7 are ortho or para substituents, independently selected from the group consisting of H, OH, C1-C6 alkyl, C1-C6 alkoxy, C7-C9 aralkoxy, C2-C7 alkanoyloxy, C1-C6 alkylmercapto (sic), halo, or CF3; R8 is H or C1-C6 alkyl; p is 0, 1, 2, 3 or 4; and R9 is H or C1-C6 alkyl]. Reaction of phenylacetonitriles II with cycloalk(an/en)ones III in the presence of a non-organometallic base catalyst IV or V, in the presence or absence of a reaction solvent, gives I [wherein: A is (CH2)n where n is 2 to 4; B is (CH2)m where m is 2 to 5; X is CH2, O, NH or NR', where R' is C1-C4 alkyl or acyl, or an alkyl supporting polymer; and each of R1 to R4 is independently H, alkyl, cycloalkyl, or an alkyl or cycloalkyl supporting polymer, and all of R1 to R4 are not H; R5 is alkyl, cycloalkyl, or an alkyl or cycloalkyl supporting polymer; and where R9 is an alkyl, the alkyl group is introduced by alkylation]. The products, such as IV, are useful intermediates for antidepressants such as venlafaxine. Known methods relying upon organometallic bases such as n-BuLi are expensive, at risk of fire or explosion, give low yields, and are impractical on an industrial scale. In contrast, the invention method is simple, economical, scalable to industrial production, safe, and environmentally friendly. Only small, catalytic amts. of the base are needed, and use of organic solvents is avoided. Both yields and **purity** of products are high. For instance, solventless reaction of 0.68 mol p-methoxyphenylacetonitrile with 1.02 mol cyclohexanone in the presence of 0.21 mol DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) for 48 h at 15-20°, followed by addition of 1N HCl to acid pH and stirring for 1 h at room temperature, gave IV in 84% yield by simple precipitation and filtration, m. 123.7°. The same procedure with only 0.1 equiv DBU and a reaction time of 6 days gave 90.5% yield. In contrast, a standard, more complex preparation of using n-BuLi in THF gave only 34.2% yield of lower-**purity** IV. Another preparation using LDA (from n-BuLi and diisopropylamine) gave 79% yield of IV, but required a large amount of toluene as solvent.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB An improved process for the preparation of cyanobenzylated cyclohexanol derivs. and analogs I is claimed [wherein: R6 and R7 are ortho or para substituents, independently selected from the group consisting of H, OH,

C1-C6 alkyl, C1-C6 alkoxy, C7-C9 aralkoxy, C2-C7 alkanoyloxy, C1-C6 alkylmercapto (sic), halo, or CF3; R8 is H or C1-C6 alkyl; p is 0, 1, 2, 3 or 4; and R9 is H or C1-C6 alkyl]. Reaction of phenylacetonitriles II with cycloalk(an/en)ones III in the presence of a non-organometallic base catalyst IV or V, in the presence or absence of a reaction solvent, gives I [wherein: A is (CH2)n where n is 2 to 4; B is (CH2)m where m is 2 to 5; X is CH2, O, NH or NR', where R' is C1-C4 alkyl or acyl, or an alkyl supporting polymer; and each of R1 to R4 is independently H, alkyl, cycloalkyl, or an alkyl or cycloalkyl supporting polymer, and all of R1 to R4 are not H; R5 is alkyl, cycloalkyl, or an alkyl or cycloalkyl supporting polymer; and where R9 is an alkyl, the alkyl group is introduced by alkylation]. The products, such as IV, are useful intermediates for antidepressants such as venlafaxine. Known methods relying upon organometallic bases such as n-BuLi are expensive, at risk of fire or explosion, give low yields, and are impractical on an industrial scale. In contrast, the invention method is simple, economical, scalable to industrial production, safe, and environmentally friendly. Only small, catalytic amts. of the base are needed, and use of organic solvents is avoided. Both yields and **purity** of products are high. For instance, solventless reaction of 0.68 mol p-methoxyphenylacetonitrile with 1.02 mol cyclohexanone in the presence of 0.21 mol DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) for 48 h at 15-20°, followed by addition of 1N HCl to acid pH and stirring for 1 h at room temperature, gave IV in 84% yield by simple precipitation and filtration, m. 123.7°. The same procedure with only 0.1 equiv DBU and a reaction time of 6 days gave 90.5% yield. In contrast, a standard, more complex preparation of using n-BuLi in THF gave only 34.2% yield of lower-**purity** IV. Another preparation using LDA (from n-BuLi and diisopropylamine) gave 79% yield of IV, but required a large amount of toluene as solvent.

IT **93413-69-5P**, Venlafaxine
RL: PNU (Preparation, unclassified); PREP (Preparation)
(intermediates for; improved process for preparation of [cyano(methoxyphenyl)methyl]cyclohexanol and analogs from phenylacetonitriles and cyclohexanone using non-organometallic base catalysts)

L8 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:928278 CAPLUS
DN 138:8362
TI Preparation of polymorphs of venlafaxine hydrochloride
IN Dolitzky, Ben-zion; Aronhime, Judith; Wizel, Shlomit; Nisnevich, Gennady A.
PA Israel
SO U.S. Pat. Appl. Publ., 18 pp., Cont.-in-part of U.S. Provisional Ser. No. 241,577.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002183553	A1	20021205	US 2001-428	20011130
	US 2002143211	A1	20021003	US 2001-45510	20011019
	WO 2003048082	A2	20030612	WO 2002-US37268	20021120

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ,

MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-241577P P 20001019
US 2000-258861P P 20001229
US 2001-278721P P 20010326
US 2001-292469P P 20010521
US 2001-428 A 20011130

AB The present invention relates to essentially pure venlafaxine and a process of preparation The present invention also relates to solvate forms of venlafaxine-HCl and the process of preparation thereof. Furthermore, the present invention provides a novel process for preparing venlafaxine-HCl from venlafaxine comprising the steps of preparing a mixture of venlafaxine with acetone, and exposing the mixture to gaseous HCl. The crude venlafaxine-HCl (15.0 g) was triturated with acetone (about 60.0 g) for about 1 h at about 60° and for about 1 h at about 0°, filtered off, washed with cold acetone and dried upon stirring under reduced pressure at about 50° to a constant weight to give about 14.8 g (about 93.2%) of venlafaxine-HCl as white crystals (Form I) with a **purity** of about 99.95% (HPLC).

AB The present invention relates to essentially pure venlafaxine and a process of preparation The present invention also relates to solvate forms of venlafaxine-HCl and the process of preparation thereof. Furthermore, the present invention provides a novel process for preparing venlafaxine-HCl from venlafaxine comprising the steps of preparing a mixture of venlafaxine with acetone, and exposing the mixture to gaseous HCl. The crude venlafaxine-HCl (15.0 g) was triturated with acetone (about 60.0 g) for about 1 h at about 60° and for about 1 h at about 0°, filtered off, washed with cold acetone and dried upon stirring under reduced pressure at about 50° to a constant weight to give about 14.8 g (about 93.2%) of venlafaxine-HCl as white crystals (Form I) with a **purity** of about 99.95% (HPLC).

IT **93413-69-5P**, Venlafaxine
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of polymorphs of venlafaxine hydrochloride)

L8 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:905806 CAPLUS
DN 137:389168
TI Delivery of antidepressants through an inhalation route
IN Rabinowitz, Joshua D.; Zaffaroni, Alejandro C.
PA Alexza Molecular Delivery Corporation, USA
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 21

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002094232	A1	20021128	WO 2002-US15765	20020516

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,

BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2003017115 A1 20030123 US 2002-146516 20020513
WO 2003026631 A1 20030403 WO 2002-US18543 20020513
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2003007933 A1 20030109 US 2002-150267 20020515
US 2003007934 A1 20030109 US 2002-150268 20020515
US 2003017117 A1 20030123 US 2002-151596 20020516
US 2003206869 A1 20031106 US 2002-151626 20020516
US 2003017116 A1 20030123 US 2002-150857 20020517
US 2003021753 A1 20030130 US 2002-150591 20020517
US 2003005924 A1 20030109 US 2002-152652 20020520
US 2003012740 A1 20030116 US 2002-153139 20020520
US 2003017118 A1 20030123 US 2002-152639 20020520
US 2003021754 A1 20030130 US 2002-152640 20020520
US 2003012737 A1 20030116 US 2002-153311 20020521
US 2003015189 A1 20030123 US 2002-153831 20020521
US 2003017119 A1 20030123 US 2002-153839 20020521
US 2003017120 A1 20030123 US 2002-155703 20020522
US 2003021755 A1 20030130 US 2002-155705 20020522
US 2003000518 A1 20030102 US 2002-155097 20020523
US 2003015190 A1 20030123 US 2002-154594 20020523
US 2003017114 A1 20030123 US 2002-154765 20020523
PRAI US 2001-294203P P 20010524
US 2001-317479P P 20010905

AB The present invention relates to the delivery of antidepressants through an inhalation route, specifically, to aerosols containing an antidepressant that are used in inhalation therapy. An aerosol composition comprises particles containing at least 5%, preferably 10%, of an antidepressant to be delivered to a mammal through an inhalation route. A method for preparation of aerosol comprises (a) heating a composition containing an antidepressant drug to form a vapor, and (b) allowing the vapor to cool, thereby forming a condensation aerosol comprising particles, which is inhaled by the mammal. A kit for delivering an antidepressant drug through an inhalation route to a mammal is provided comprising (a) a composition containing at least 5% of the drug, and (b) a device that forms aerosol from the composition, the device comprising (i) an element for heating the composition to form a vapor, (ii) an element allowing the vapor to cool and form an aerosol, and (iii) an element permitting the mammal to inhale the aerosol. For example, an antidepressant drug was coated on aluminum foil and the coated foil was heated using a halogen bulb to afford thermal vapor (including aerosol). The **purity** of aerosol was dependent on the coat thickness, i.e., a linear decrease in film thickness is associated with a linear decrease in impurities.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The present invention relates to the delivery of antidepressants through an inhalation route, specifically, to aerosols containing an antidepressant that are used in inhalation therapy. An aerosol composition comprises particles containing at least 5%, preferably 10%, of an antidepressant to be delivered to a mammal through an inhalation route. A method for preparation of aerosol comprises (a) heating a composition containing an antidepressant drug to form a vapor, and (b) allowing the vapor to cool, thereby forming a

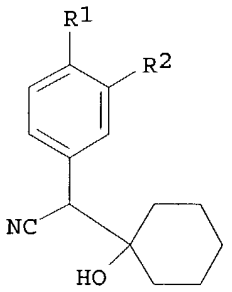
condensation aerosol comprising particles, which is inhaled by the mammal. A kit for delivering an antidepressant drug through an inhalation route to a mammal is provided comprising (a) a composition containing at least 5% of the drug, and (b) a device that forms aerosol from the composition, the device comprising (i) an element for heating the composition to form a vapor, (ii) an element allowing the vapor to cool and form an aerosol, and (iii) an element permitting the mammal to inhale the aerosol. For example, an antidepressant drug was coated on aluminum foil and the coated foil was heated using a halogen bulb to afford thermal vapor (including aerosol). The **purity** of aerosol was dependent on the coat thickness, i.e., a linear decrease in film thickness is associated with a linear decrease in impurities.

IT 50-49-7, Imipramine 58-39-9, Perphenazine 72-69-5 99-66-1, Valproic acid 155-09-9, Tranylcypromine 303-49-1, Clomipramine 438-60-8, Protryptyline 739-71-9, Trimipramine 1668-19-5, Doxepin 10262-69-8, Maprotiline 14028-44-5, Amoxapine 19794-93-5, Trazodone 34911-55-2, Bupropion 54739-18-3, Fluvoxamine 54910-89-3, Fluoxetine 59729-33-8, Citalopram 61869-08-7, Paroxetine 79617-96-2, Sertraline 83366-66-9, Nefazodone 85650-52-8, Mirtazapine **93413-69-5**, Venlafaxine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(kit for delivery of antidepressants through inhalation route)

L8 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:658793 CAPLUS
DN 137:185318
TI Process for the preparation of 1-[cyano(aryl)methyl]cyclohexanols by the aldol condensation of phenylacetonitriles with cyclohexanone
IN Chavan, Subhash Prataprao; Kamat, Subhash Krishnaji; Sivadasan, Latha; Balakrishnan, Kamalam; Khobragade, Dushant Anandrao; Thottapillil, Ravindranathan; Gurjar, Mukund Keshao; Kalkote, Uttam Ramrao
PA Council of Scientific and Industrial Research, India
SO U.S. Pat. Appl. Publ., 4 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002120164	A1	20020829	US 2001-796084	20010228
	US 6504044	B2	20030107		
	EP 1238967	A1	20020911	EP 2001-301840	20010228
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	US 2001-796084	A	20010228		

OS CASREACT 137:185318
GI



I

AB The invention relates to a process for the preparation of 1-[(cyano)arylmethyl]cyclohexanols [I; (a) R1 = H, R2 = H; (b) R1 = OMe, R2 = H; (c) R1 = OMe, R2 = OMe; (d) R1 = OMe, R2 = cyclopentyloxy; e.g., 2-(1-hydroxycyclohexyl)-2-phenylacetonitrile] in high yield and selectivity by the aldol reaction of cyclohexanone with the carbanions of a correspondingly substituted phenylacetonitrile (e.g., phenylacetonitrile) in the presence of a catalytic quantity of a base (e.g., sodium hydroxide) at 0-15° for 15-120 min, and isolating and **purifying** the I compound by crystallization More particularly the invention relates to the preparation of 1-[cyano(4-methoxyphenyl)methyl]cyclohexanol [I; R1 = OMe, R2 = H], a key intermediate for the synthesis of Venlafaxine.

AB The invention relates to a process for the preparation of 1-[(cyano)arylmethyl]cyclohexanols [I; (a) R1 = H, R2 = H; (b) R1 = OMe, R2 = H; (c) R1 = OMe, R2 = OMe; (d) R1 = OMe, R2 = cyclopentyloxy; e.g., 2-(1-hydroxycyclohexyl)-2-phenylacetonitrile] in high yield and selectivity by the aldol reaction of cyclohexanone with the carbanions of a correspondingly substituted phenylacetonitrile (e.g., phenylacetonitrile) in the presence of a catalytic quantity of a base (e.g., sodium hydroxide) at 0-15° for 15-120 min, and isolating and **purifying** the I compound by crystallization More particularly the invention relates to the preparation of 1-[cyano(4-methoxyphenyl)methyl]cyclohexanol [I; R1 = OMe, R2 = H], a key intermediate for the synthesis of Venlafaxine.

IT **93413-69-5P**
RL: PNU (Preparation, unclassified); PREP (Preparation)
(process for preparation of key intermediate for preparation of Venlafaxine)

L8 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:560101 CAPLUS
DN 137:74569
TI Simultaneous determination of viloxazine, venlafaxine, imipramine, desipramine, sertraline, and amoxapine in whole blood: Comparison of two extraction/cleanup procedures for capillary gas chromatography with nitrogen-phosphorus detection
AU Martinez, M. A.; Sanchez de la Torre, C.; Almarza, E.
CS Department of Chemistry, National Institute of Toxicology, Ministry of Justice, Madrid, 28002, Spain
SO Journal of Analytical Toxicology (2002), 26(5), 296-302
CODEN: JATOD3; ISSN: 0146-4760
PB Preston Publications
DT Journal
LA English
AB A comparative study for the simultaneous gas chromatog. (GC) resolution and detection of the six antidepressants viloxazine, venlafaxine, imipramine, desipramine, sertraline, and amoxapine in whole blood at concentration levels of 100-2000 ng/mL was developed. Two extraction/cleanup anal. procedures were compared regarding their recovery, precision, sensitivity and matrix **purifn**. efficiency. The first procedure consists of the employment of Chem Elut columns (diatomaceous earth) and is based on the principle of liquid-solid absorption extraction that is closely related to conventional liquid-liquid extraction The second focuses on the use of Bond Elut Certify columns and a mixed SPE, reversed-phase and cation-exchange sorbent, more recently developed for the market. Each procedure required 2.0 mL of whole blood extraction and injection into a capillary GC equipped with a nitrogen-phosphorus detector. Mepivacaine was used as the extraction standard (surrogate), and prazepam was used as the chromatog. standard No interferences were found, and the time for the chromatog. anal. was 16 min for one sample. Recoveries of the compds. using Chem Elut columns at 500

ng/mL were in the range of 28-74% with intra-assay and interassay precisions of less than 7% and 19%, resp. Limits of detection (LOD) and quantitation (LOQ) ranged from 39 to 153 ng/mL and from 128 to 504 ng/mL, resp. Recoveries of the compds. using Bond Elut Certify columns at 500 ng/mL were in the range of 64-86% with intra-assay and interassay precisions of less than 4% and 10%, resp. LODs and LOQs ranged from 21 to 100 ng/mL and from 70 to 330 ng/mL, resp. An excellent linearity was observed with both procedures from the LOQs up to 2000 ng/mL. The use of the reversed-phase and cation-exchange sorbent Bond Elut Certify showed advantages compared with Chem Elut columns for the screening of these antidepressants such as higher recoveries, cleaner exts., better sensitivity, better precision, and less solvent consumption and disposal. (c) 2002 Preston Publications.

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A comparative study for the simultaneous gas chromatog. (GC) resolution and detection of the six antidepressants viloxazine, venlafaxine, imipramine, desipramine, sertraline, and amoxapine in whole blood at concentration levels of 100-2000 ng/mL was developed. Two extraction/cleanup anal. procedures were compared regarding their recovery, precision, sensitivity and matrix **purifn**. efficiency. The first procedure consists of the employment of Chem Elut columns (diatomaceous earth) and is based on the principle of liquid-solid absorption extraction that is closely related to conventional liquid-liquid extraction The second focuses on the use of Bond Elut Certify columns and a mixed SPE, reversed-phase and cation-exchange sorbent, more recently developed for the market. Each procedure required 2.0 mL of whole blood extraction and injection into a capillary GC equipped with a nitrogen-phosphorus detector. Mepivacaine was used as the extraction standard (surrogate), and prazepam was used as the chromatog. standard No interferences were found, and the time for the chromatog. anal. was 16 min for one sample. Recoveries of the compds. using Chem Elut columns at 500 ng/mL were in the range of 28-74% with intra-assay and interassay precisions of less than 7% and 19%, resp. Limits of detection (LOD) and quantitation (LOQ) ranged from 39 to 153 ng/mL and from 128 to 504 ng/mL, resp. Recoveries of the compds. using Bond Elut Certify columns at 500 ng/mL were in the range of 64-86% with intra-assay and interassay precisions of less than 4% and 10%, resp. LODs and LOQs ranged from 21 to 100 ng/mL and from 70 to 330 ng/mL, resp. An excellent linearity was observed with both procedures from the LOQs up to 2000 ng/mL. The use of the reversed-phase and cation-exchange sorbent Bond Elut Certify showed advantages compared with Chem Elut columns for the screening of these antidepressants such as higher recoveries, cleaner exts., better sensitivity, better precision, and less solvent consumption and disposal. (c) 2002 Preston Publications.

IT 50-47-5, Desipramine 50-49-7, Imipramine 14028-44-5, Amoxapine 46817-91-8, Viloxazine 79617-96-2, Sertraline **93413-69-5**, Venlafaxine
RL: ANT (Analyte); ANST (Analytical study)
(viloxazine, venlafaxine, imipramine, desipramine, sertraline, and amoxapine simultaneous determined in blood by liquid-liquid and liquid-solid extraction for capillary GC with nitrogen-phosphorus detection)

L8 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:449451 CAPLUS
DN 137:24386
TI Crystalline venlafaxine base and novel polymorphs of venlafaxine hydrochloride and processes for their preparation
IN Dolitzky, Ben-Zion; Aronhime, Judith; Weizel, Shlomit; Nisnevish, Gennady
PA Teva Pharmaceutical Industries, Ltd., Israel; Teva Pharmaceuticals USA,

Inc.
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002045658	A2	20020613	WO 2001-US51017	20011019
	WO 2002045658	A3	20030116		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2002041764	A5	20020618	AU 2002-41764	20011019
	US 2002143211	A1	20021003	US 2001-45510	20011019
	EP 1334082	A2	20030813	EP 2001-988460	20011019
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	NO 2003001743	A	20030618	NO 2003-1743	20030415
PRAI	US 2000-241577P	P	20001019		
	US 2000-258861P	P	20001229		
	US 2001-278721P	P	20010326		
	US 2001-292469P	P	20010521		
	WO 2001-US51017	W	20011019		

AB The present invention relates to preparation of novel essentially pure venlafaxine and solvate forms of venlafaxine hydrochloride. Furthermore, the present invention provides a novel process for preparing venlafaxine hydrochloride from venlafaxine; the process comprises the steps of: (i) preparing a mixture of venlafaxine with acetone; and (ii) exposing the mixture in gaseous hydrochloric acid. For example, crystalline venlafaxine free base was prepared from N,N-didesmethyl venlafaxine hydrochloride and extracted with heptane. The venlafaxine base obtained reacted with hydrochloric acid and crystallized to generate venlafaxine hydrochloride of **purity** > 97%. Crystalline venlafaxine hydrochloride was then used for preparation of solvate and polymorphic forms with solvent/antisolvent.

AB The present invention relates to preparation of novel essentially pure venlafaxine and solvate forms of venlafaxine hydrochloride. Furthermore, the present invention provides a novel process for preparing venlafaxine hydrochloride from venlafaxine; the process comprises the steps of: (i) preparing a mixture of venlafaxine with acetone; and (ii) exposing the mixture in gaseous hydrochloric acid. For example, crystalline venlafaxine free base was prepared from N,N-didesmethyl venlafaxine hydrochloride and extracted with heptane. The venlafaxine base obtained reacted with hydrochloric acid and crystallized to generate venlafaxine hydrochloride of **purity** > 97%. Crystalline venlafaxine hydrochloride was then used for preparation of solvate and polymorphic forms with solvent/antisolvent.

IT **93413-69-5P**, Venlafaxine
RL: PEP (Physical, engineering or chemical process); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(preparation of crystalline venlafaxine base and novel polymorphs of venlafaxine

hydrochloride)

L8 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:241329 CAPLUS
DN 136:284433
TI Administration of phosphodiesterase inhibitors for the treatment of premature ejaculation
IN Wilson, Leland F.; Doherty, Paul C.; Place, Virgil A.; Smith, William L.; Abdel-Hamid, Abdou Ali Ibrahim Aboubakr
PA USA
SO U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. Ser. No. 467,094.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002037828	A1	20020328	US 2001-888250	20010621
	US 6403597	B2	20020611		
	US 6037346	A	20000314	US 1998-181070	19981027
	US 6548490	B1	20030415	US 1999-467094	19991210
	WO 2003000343	A2	20030103	WO 2002-US9415	20020325

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI	US 1997-958816	B2	19971028
	US 1998-181070	A2	19981027
	US 1999-467094	A2	19991210
	US 2001-888250	A	20010621

AB A method is provided for treatment of premature ejaculation by administration of a phosphodiesterase inhibitor, e.g., an inhibitor of a Type III, Type IV, or Type V phosphodiesterase. In a preferred embodiment, administration is on as "as needed" basis, i.e., the drug is administered immediately or several hours prior to sexual activity. Pharmaceutical formulations and packaged kits are also provided. Zaprinast 1.0, mannitol 1.0, microcryst. cellulose 2.0, and magnesium stearate 10 mg are blended in a suitable mixer and then compressed into sublingual tablets. Each sublingual tablet contains 10 mg zaprinast.
IT 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 51-12-7, Nialamide 51-71-8, Phenelzine 55-21-0D, Benzamide, derivs. 58-32-2, Dipyridamole 58-55-9, Theophylline, biological studies 58-74-2, Papaverine 59-63-2, Isocarboxazid 69-89-6D, Xanthine, derivs. 72-69-5, Nortriptyline 73-22-3, Tryptophan, biological studies 83-67-0, Theobromine 91-20-3D, Naphthalene, derivs. 92-52-4D, Biphenyl, derivs. 95-15-8D, Benzothiophene, derivs. 98-89-5D, Cyclohexanecarboxylic acid, derivs. 113-45-1, Methylphenidate 113-53-1, Dothiepin 120-73-0D, **Purine**, derivs. 138-56-7, Trimethobenzamide 155-09-9, Tranylcypromine 271-89-6D, Benzofuran, derivs. 302-40-9, Benactyzine 303-49-1, Clomipramine 315-72-0, Opipramol 438-60-8, Protriptyline 475-81-0, S-(+)-Glaucine 616-45-5D, 2-Pyrrolidinone, derivs. 739-71-9, Trimipramine 1668-19-5, Doxepin 4350-09-8, Oxitriptan 4498-32-2, Dibenzepin 4757-55-5, Dimetacrine 5118-29-6, Melitracen 5560-72-5, Iprindole 6493-05-6, Pentoxifylline 10262-69-8, Maprotiline 10321-12-7, Propizepine 12794-10-4D, Benzodiazepine, derivs. 14028-44-5, Amoxapine 14611-51-9, Selegiline 15301-93-6, Tofenacin 17780-72-2, Clorgyline 19794-93-5,

Trazodone 21730-16-5, Metapramine 23047-25-8, Lofepramine 24219-97-4, Mianserin 24526-64-5, Nomifensine 24701-51-7, Demexiptiline 25905-77-5, Minaprine 26629-87-8, Oxaflozane 28822-58-4, IBMX 29218-27-7, Toloxatone 31721-17-2, Quinupramine 32359-34-5, Medifoxamine 34911-55-2, Bupropion 35941-65-2, Butriptyline 37762-06-4, Zaprinast 42971-09-5, Vinpocetine 46817-91-8, Viloxazine 50847-11-5, Ibudilast 51022-77-6, Etazolate 52942-31-1, Etoperidone 54739-18-3, Fluvoxamine 54739-19-4, Clovoxamine 54910-89-3, Fluoxetine 56433-44-4, Oxaprotiline 56611-65-5, Phthalazinol 56775-88-3, Zimeldine 57262-94-9, Setiptiline 57574-09-1, Amineptine 59729-33-8, Citalopram 59859-58-4, Femoxetine 60719-84-8, Amrinone 60762-57-4, Pirlindole 61413-54-5, Rolipram 61869-08-7, Paroxetine 62473-79-4, Teniloxazine 63638-91-5, Brofaromine 66208-11-5, Ifoxetine 66327-51-3, Furazlocillin 66834-24-0, Cianopramine 68475-42-3, Anagrelide 70018-51-8, Quazinone 71320-77-9, Moclobemide 72714-74-0, Viqualine 72797-41-2, Tianeptine 74150-27-9, Pimobendan 76496-68-9, Levoprotiline 78033-10-0 78351-75-4 78415-72-2, Milrinone 79030-08-3D, Griseolic acid, derivs. 79617-96-2, Sertraline 79855-88-2, Trequinsin 80410-36-2, Fezolamine 81098-60-4, Cisapride 83366-66-9, Nefazodone 83863-69-8, NorCisapride 85650-52-8, Mirtazapine 86315-52-8, Isomazole 89565-68-4, Tropisetron 90182-92-6, Zacopride 90697-57-7, Motapizone 92623-85-3, Milnacipran **93413-69-5**, Venlafaxine 94192-59-3, Lixazinone 99614-02-5, Ondansetron 102670-46-2, Batanopride 106650-56-0, Sibutramine 106730-54-5, Olprinone 109889-09-0, Granisetron 112018-01-6, Bemoradan 115344-47-3, Siguazodan 115956-12-2, Dolasetron 116539-59-4, Duloxetine 119356-77-3, Dapoxetine 121588-75-8, Amesergide 139145-27-0 139755-83-2, Sildenafil 147676-63-9 150452-18-9 167298-74-0, Sch-51866 167298-97-7 168464-34-4 168464-60-6 171599-83-0, Sildenafil citrate 184147-55-5D, derivs. 212498-37-8 224157-99-7 224785-90-4, Vardenafil 330784-28-6 330784-47-9 330785-79-0 405508-89-6 405551-89-5, FR 229934
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(administration of phosphodiesterase inhibitors for treatment of premature ejaculation)

L8 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:151557 CAPLUS
DN 136:200009
TI One-pot process for the preparation of Venlafaxine from 1-[cyano(4-methoxyphenyl)methyl]cyclohexanol
IN Chavan, Subhash Prataprao; Kamat, Subhash Krishnaji; Sivadasan, Latha; Balakrishnan, Kamalam; Khobragade, Dushant Anandrao; Thottapillil, Ravindranathan; Gurjar, Mukund Keshao; Kalkote, Uttam Ramrao
PA Council of Scientific and Industrial Research, India
SO U.S., 4 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6350912	B1	20020226	US 2001-796082	20010228
EP 1238965	A1	20020911	EP 2001-301839	20010228

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRAI US 2001-796082 A 20010228
OS CASREACT 136:200009
AB A one-pot process for the preparation of venlafaxine [i.e., 2-[dimethylamino(4-methoxyphenyl)ethyl]-cyclohexanol] comprises hydrogenating 1-[cyano(4-methoxyphenyl)methyl]cyclohexanol with a formylating agent (e.g, formalin) in a protic solvent (e.g., methanol) in

the presence of a catalyst (e.g., Raney nickel) at 30-60°/100-400 psi for 6-16 h, removing the catalyst by filtration, and isolating and **purifying** the Venlafaxine.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A one-pot process for the preparation of venlafaxine [i.e., 2-[dimethylamino(4-methoxyphenyl)ethyl]-cyclohexanol] comprises hydrogenating 1-[cyano(4-methoxyphenyl)methyl]cyclohexanol with a formylating agent (e.g, formalin) in a protic solvent (e.g., methanol) in the presence of a catalyst (e.g., Raney nickel) at 30-60°/100-400 psi for 6-16 h, removing the catalyst by filtration, and isolating and **purifying** the Venlafaxine.

IT **93413-69-5P**, Venlafaxine
RL: SPN (Synthetic preparation); PREP (Preparation)
(one-pot process for the preparation of Venlafaxine from 1-[cyano(4-methoxyphenyl)methyl]cyclohexanol)

L8 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:143294 CAPLUS
DN 136:189323
TI Preparation and pharmaceutical formulation of enantiomers of O-desmethyl venlafaxine
IN Yardley, John P.; Asselin, Andre A.
PA American Home Products Corporation, USA
SO U.S. Pat. Appl. Publ., 8 pp., Cont. of U.S. Ser. No. 590,741, abandoned.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002022662	A1	20020221	US 2001-957908	20010921
	US 2002161055	A1	20021031	US 2002-154994	20020523
	US 2003149112	A1	20030807	US 2003-373145	20030224
PRAI	US 1999-183029P	P	19990615		
	US 2000-590741	B1	20000608		
	US 2001-957908	A1	20010921		
	US 2002-154994	B1	20020523		

AB This invention provides pharmaceutically active enantiomers of the venlafaxine metabolite O-Desmethyl venlafaxine, R(-)-4-[2-(Dimethylamnino)-1-(1-hydroxycyclo-hexyl)ethyl]phenol or R(-)1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclo-hexanol (I), and S(+)-1-[2-(Dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol or S(+)-4-[2-(Dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenol, or one or more pharmaceutically acceptable salts or salt hydrates thereof, as well as pharmaceutical compns. utilizing these enantiomers and methods of using the enantiomers to treat, inhibit or control central nervous system disorders. To a solution of 1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol free base (preparation given) in EtOAc at room temperature was added at once to a solution of (+)-Di-para toluoyl-D-tartaric acid-monohydrate (DT(-)T) and was stirred at room temperature for 1 h. The resulting precipitate was filtered off, washed with EtOAc , dried overnight at 35° in a vacuum oven to provide crude R(-)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)-ethyl]cyclohexanol DT(-)T salt (yield = 92.8%) as a white solid. The solid was recrystd., and treated with sodium hydroxide solution to obtain I base which was separated and **purified**. Neurotransmitter uptake inhibition activity of the enantiomers were studied in rats. Pharmaceutical formulations of different enantiomers are disclosed.

AB This invention provides pharmaceutically active enantiomers of the venlafaxine metabolite O-Desmethyl venlafaxine, R(-)-4-[2-(Dimethylamnino)-

1-(1-hydroxycyclo-hexyl)ethyl]phenol or R(-)1-[2-(dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclo-hexanol (I), and S(+)-1-[2-(Dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol or S(+)-4-[2-(Dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenol, or one or more pharmaceutically acceptable salts or salt hydrates thereof, as well as pharmaceutical compns. utilizing these enantiomers and methods of using the enantiomers to treat, inhibit or control central nervous system disorders. To a solution of 1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol free base (preparation given) in EtOAc at room temperature was added at once to a solution of (+)-Di-para toluoyl-D-tartaric acid-monohydrate (DT(-)T) and was stirred at room temperature for 1 h. The resulting precipitate was filtered off, washed with EtOAc , dried overnight at 35° in a vacuum oven to provide crude R(-)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)-ethyl]cyclohexanol DT(-)T salt (yield = 92.8%) as a white solid. The solid was recrystd., and treated with sodium hydroxide solution to obtain I base which was separated and **purified**. Neurotransmitter uptake inhibition activity of the enantiomers were studied in rats. Pharmaceutical formulations of different enantiomers are disclosed.

IT **93413-69-5P** 99300-78-4P 142761-12-4P 272788-00-8P
313471-75-9P 313471-76-0P 313474-92-9P 400052-85-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and pharmaceutical formulation of enantiomers of desmethyl venlafaxine)

L8 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1998:323132 CAPLUS
DN 129:23447
TI A method for treating tension-type headache
IN Olesen, Jes; Bendtsen, Lars; Jensen, Rigmor; Madsen, Ulf
PA Olesen, Jes, Den.; Bendtsen, Lars; Jensen, Rigmor; Madsen, Ulf
SO PCT Int. Appl., 142 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9819674	A2	19980514	WO 1997-DK502	19971104
	WO 9819674	A3	19980716		
	W: AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ, DE, DE, DK, DK, EE, ES, FI, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9748632	A1	19980529	AU 1997-48632	19971104
	AU 734490	B2	20010614		
	EP 1011656	A2	20000628	EP 1997-911150	19971104
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	EP 1132082	A1	20010912	EP 2000-204625	19971104
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	US 6284794	B1	20010904	US 1999-304115	19990504
	US 2002072543	A1	20020613	US 2001-941855	20010830
	US 6649605	B2	20031118		

PRAI DK 1996-1243 A 19961105
US 1996-30294P P 19961105
EP 1997-911150 A3 19971104
WO 1997-DK502 W 19971104
US 1998-85413P P 19980514
US 1999-304115 A3 19990504

AB Tension-type headache is treated by interacting with neuronal transmission in relation to pain in connection with headache in a way which prevents or decreases sensitization of second order nociceptive neurons. In particular, treatment is performed by administration of an effective amount of a substance which prevents or decreases central sensitization. Important examples of such substances are substances which interact with glutamate neurotransmission, such as glutamate receptor antagonists. Other examples are e.g. substances which interact with nitric oxide, such as nitric oxide synthase (NOS) inhibitors. According to a broader aspect of the invention, tension-type headache is treated by administration of substances which are effective in preventing or decreasing pain in connection with tension-type headache. An addnl. aspect of the invention relates to treatment of tension-type headache by administration of substances which substantially inhibit the activity of NOS. Evidence for central sensitization in chronic myofascial pain, as well as mechanisms of spontaneous tension-type headaches, are also described. Gabapentin and dextromethorphan had a prophylactic effect on chronic tension-type headaches.

IT **Purinoceptor** antagonists
(A2; tension-type headache treatment)

IT 50-47-5, Desipramine 50-47-5D, Desipramine, derivs. 50-48-6, Amitriptyline 50-48-6D, Amitriptyline, derivs. 50-49-7, Imipramine 50-49-7D, Imipramine, derivs. 56-12-2D, γ-Aminobutyric acid, derivs. 56-40-6D, Glycine, derivs., biological studies 57-41-0, Phenytoin 57-41-0D, Phenytoin, derivs. 58-32-2, Dipyridamole 58-32-2D, Dipyridamole, derivs. 58-61-7D, Adenosine, derivs., biological studies 69-89-6D, Xanthine, derivs. 74-79-3D, L-Arginine, derivs., biological studies 91-19-0D, Quinoxaline, derivs. 92-52-4D, Biphenyl, derivs. 108-91-8D, Cyclohexylamine, aryl derivs. 110-85-0D, Piperazine, diacidic derivs., biological studies 110-89-4D, Piperidine, derivs., biological studies 110-89-4D, Piperidine, diacidic derivs., biological studies 120-72-9D, Indole, derivs. 125-71-3, Dextromethorphan 125-71-3D, Dextromethorphan, derivs. 137-58-6, Lidocaine 137-58-6D, Lidocaine, derivs. 253-52-1D, Phthalazine, derivs. 256-96-2D, 5H-Dibenz[b,f]azepine, derivs. 271-44-3D, Indazole, derivs. 288-32-4D, Imidazole, derivs. 289-95-2D, Pyrimidine, derivs. 298-46-4, Carbamazepine 298-46-4D, Carbamazepine, derivs. 301-15-5, Synthalin 301-15-5D, Synthalin, derivs. 372-75-8D, Citrulline, derivs. 461-72-3D, Hydantoin, derivs. 492-27-3D, Kynurenic acid, derivs. 498-94-2, Isonipecotic acid 498-94-2D, Isonipecotic acid, derivs. 498-95-3D, Nipecotic acid, derivs. 498-96-4, Guvacine 498-96-4D, Guvacine, derivs. 505-66-8D, Homopiperazine, derivs. 598-41-4D, derivs. 768-94-5D, Adamantanamine, derivs. 1744-22-5, Riluzole 1744-22-5D, Riluzole, derivs. 2149-70-4 2149-70-4D, derivs. 2835-06-5D, derivs. 2942-42-9, 7-Nitroindazole 2942-42-9D, 7-Nitroindazole, derivs. 4205-90-7, Clonidine 4205-90-7D, Clonidine, derivs. 4673-26-1 4673-26-1D, derivs. 5777-20-8D, 3-Hydroxyisoxazole, derivs. 6740-88-1, Ketamine 6740-88-1D, Ketamine, derivs. 7361-61-7, Xylazine 7361-61-7D, Xylazine, derivs. 12654-97-6D, Triazine, derivs. 13598-36-2D, Phosphonic acid, aryl phosphonic esters 14114-46-6, DMPX 14114-46-6D, DMPX, derivs. 15574-96-6, Pizotyline 15574-96-6D, Pizotyline, derivs. 17035-90-4 17035-90-4D, derivs. 18000-24-3, 7-Chlorokynurenic acid 18000-24-3D, 7-Chlorokynurenic acid, derivs. 19982-08-2, Memantine 19982-08-2D, Memantine, derivs. 21730-16-5, Metapramine 21730-16-5D, Metapramine, derivs. 22059-21-8 22059-21-8D, derivs. 23052-81-5 23052-81-5D,

derivs. 23210-56-2, Ifenprodil 23210-56-2D, Ifenprodil, derivs. 24887-75-0D, Androstane, derivs. 25371-96-4 25371-96-4D, derivs. 25448-04-8D, Tetrahydroquinoline, derivs. 25451-15-4, Felbamate 25451-15-4D, Felbamate, derivs. 25983-13-5 25983-13-5D, derivs. 30315-93-6, Dimethyl-L-arginine 30315-93-6D, Dimethyl-L-arginine, derivs. 31828-71-4, Mexiletine 31828-71-4D, derivs. 35211-10-0, Norketamine 35211-10-0D, Norketamine, derivs. 35898-87-4, Dilazep 35898-87-4D, Dilazep, derivs. 36889-13-1 36889-13-1D, derivs. 38090-53-8 38090-53-8D, derivs. 38638-24-3D, Aminoimidazoline, derivs. 38886-20-3D, Aminopiperidine, derivs. 41443-28-1 41443-28-1D, derivs. 41552-82-3, N6-Cyclopentyladenosine 41552-82-3D, N6-Cyclopentyladenosine, derivs. 41708-72-9, Tocainide 41708-72-9D, Tocainide, derivs. 50903-99-6, L-NAME 50903-99-6D, L-NAME, derivs. 52468-60-7, Flunarizine 52468-60-7D, Flunarizine, derivs. 53602-00-9 53602-00-9D, derivs. 59467-70-8, Midazolam 59467-70-8D, Midazolam, derivs. 60142-96-3, Gabapentin 60142-96-3D, Gabapentin, derivs. 61869-08-7, Paroxetine 61869-08-7D, Paroxetine, derivs. 64603-90-3, Isoguvacine 64603-90-3D, Isoguvacine, derivs. 64603-91-4 64603-91-4D, derivs. 66711-21-5, Apraclonidine 66711-21-5D, Apraclonidine, derivs. 71609-37-5, (±)-cis-4-Hydroxynipecotic acid 71609-37-5D, (±)-cis-4-Hydroxynipecotic acid, derivs. 75889-62-2, Fostedil 75889-62-2D, Fostedil, derivs. 77086-22-7, MK-801 77086-22-7D, MK-801, derivs. 84057-84-1, Lamotrigine 84057-84-1D, Lamotrigine, derivs. 85375-15-1, SKF 89976A 85375-15-1D, SKF 89976A, derivs. 85650-52-8, Mirtazapine 85650-52-8D, Mirtazapine, derivs. **93413-69-5**, Venlafaxine **93413-69-5D**, Venlafaxine, derivs. 102771-26-6, GYKI 52466 102771-26-6D, GYKI 52466, derivs. 110101-66-1, Tirilazad 110101-66-1D, Tirilazad, derivs. 110347-85-8, CGS 19755 110347-85-8D, CGS 19755, derivs. 113775-47-6, Dexmedetomidine 113775-47-6D, Dexmedetomidine, derivs. 115066-14-3, CNQX 115066-14-3D, CNQX, derivs. 115103-54-3, Tiagabine 115103-54-3D, Tiagabine, derivs. 117414-74-1 117414-74-1D, derivs. 118876-58-7, NBQX 118876-58-7D, NBQX, derivs. 119431-25-3, Eliprodil 119431-25-3D, Eliprodil, derivs. 119514-66-8, Lifarizine 119514-66-8D, Lifarizine, derivs. 123931-04-4 123931-04-4D, derivs. 126453-07-4 126453-07-4D, derivs. 128298-28-2, Remacemide 128298-28-2D, Remacemide, derivs. 130308-48-4, Icatibant 130308-48-4D, Icatibant, derivs. 131417-68-0 131417-68-0D, derivs. 134052-73-6 134052-73-6D, derivs. 136529-54-9 136529-54-9D, derivs. 136623-01-3, NS-102 136623-01-3D, NS-102, derivs. 136982-36-0, CP 99,994 136982-36-0D, CP 99,994, derivs. 137433-06-8, LY 235959 137433-06-8D, LY 235959, derivs. 138449-07-7, FK 888 138449-07-7D, FK 888, derivs. 139051-78-8, L-689560 139051-78-8D, L-689560, derivs. 142001-63-6, SR-48968 142001-63-6D, SR-48968, derivs. 142326-59-8, L-701324 142326-59-8D, L-701324, derivs. 144177-30-0, WIN 51708 144177-30-0D, WIN 51708, derivs. 144665-07-6, Lubeluzole 144665-07-6D, Lubeluzole, derivs. 147750-87-6, NS-257 147750-87-6D, NS-257, derivs. 147778-05-0, L 698544 147778-05-0D, derivs. 148819-94-7 148819-94-7D, derivs. 150010-68-7, LY 215490 150010-68-7D, LY 215490, derivs. 151039-63-3, WIN 64338 151039-63-3D, WIN 64338, derivs. 151056-97-2, L 701273 151056-97-2D, derivs. 151057-13-5, L 701252 151057-13-5D, derivs. 153436-22-7D, GV 150526A, derivs. 153504-81-5, ACEA 1021 153504-81-5D, ACEA 1021, derivs. 154164-30-4, YM90K 154164-30-4D, YM90K, derivs. 156694-78-9 156694-78-9D, derivs. 156719-41-4, (S)-Methylthiocitrulline 156719-41-4D, (S)-Methylthiocitrulline, derivs. 158848-32-9, GR 159897 158848-32-9D, GR 159897, derivs. 159094-94-7, NO-711 159094-94-7D, NO-711, derivs. 168560-79-0, UPF523 168560-79-0D, UPF523, derivs. 170566-84-4, LY 303870 170566-84-4D, LY 303870, derivs. 173952-44-8, SYM 2206 190784-53-3 190784-53-3D, derivs. 207723-17-9D, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

10/290,245

(Uses)
(tension-type headache treatment)

=>

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=> e venlafaxine base/cn
E1            1     VENKATASIN/CN
E2            1     VENLAFAXINE/CN
E3            0 --> VENLAFAXINE BASE/CN
E4            1     VENLAFAXINE HYDROCHLORIDE/CN
E5            1     VENLAFAXINE O-DEMETHYLASE/CN
E6            1     VENLAFEXINE/CN
E7            1     VENMET/CN
E8            1     VENNO CYCLA 2/CN
E9            1     VENOBARBITAL/CN
E10           1     VENOCURAN/CN
E11           1     VENOFER/CN
E12           1     VENOFERRUM/CN

=> s e3
L4            0 "VENLAFAXINE BASE"/CN

=> s e4
L5            1 "VENLAFAXINE HYDROCHLORIDE"/CN

=> d rn

L5   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   99300-78-4  REGISTRY


=> s e2
L6            1 VENLAFAXINE/CN

=> d rn

L6   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   93413-69-5  REGISTRY


=>
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10/290,245 Only venlafaxine not the HCl

=> d bib abs kwic l3 600-629

L3 ANSWER 600 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:236841 CAPLUS
DN 124:307388
TI Effectiveness of venlafaxine treatment in a broad spectrum of depressed patients: A meta-analysis
AU Entsuah, A. Richard; Rudolph, Richard L.; Chitra, Rohini
CS Clinical Research and Development, Wyeth-Ayerst Research, Philadelphia, PA, 19807, USA
SO Psychopharmacology Bulletin (1995), 31(4), 759-66
CODEN: PSYBB9; ISSN: 0048-5764
PB U.S. Dep. of Health and Human Services
DT Journal
LA English
AB The effectiveness of the novel antidepressant venlafaxine was assessed in various subpopulations of depressed patients. Data from six comparable placebo-controlled, double-blind studies were pooled and analyzed (venlafaxine, n=930; placebo, n=500). Outcome variables were the Hamilton Rating Scale for Depression total score, Montgomery-Asberg Depression Rating Scale total score, and Clin. Global Impressions severity scores. Venlafaxine had notable antidepressant results in depressed patients regardless of age (although no age differences were apparent, too few patients over age 65 had been enrolled in the six studies to permit definitive conclusions), gender, presence of melancholia, and severity or duration of depression. Our anal. indicates that venlafaxine treatment is effective in a broad range of depressed patients.
IT **93413-69-5**, Venlafaxine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effectiveness of venlafaxine treatment in a broad spectrum of depressed human patients)

L3 ANSWER 601 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:236840 CAPLUS
DN 124:307387
TI Venlafaxine in depressed geriatric outpatients: An open-label clinical study
AU Khan, Arifulla; Rudolph, Richard; Baumel, Barry; Ferguson, James; Ryan, Patrick; Shrivastava, Ram
CS Medical Director, Northwest Psychiatric Institute, Kirkland, WA, 98034, USA
SO Psychopharmacology Bulletin (1995), 31(4), 753-8
CODEN: PSYBB9; ISSN: 0048-5764
PB U.S. Dep. of Health and Human Services
DT Journal
LA English
AB A 12-mo open-label clin. trial was conducted to evaluate patient acceptance and safety of venlafaxine, a novel antidepressant, in ambulatory geriatric depressed patients. The sample consisted of 58 depressed patients aged 65 yr and older who needed long-term antidepressant treatment. The setting was multiple study sites in California, Florida, New York, Utah, and Washington. All patients took venlafaxine; 52 qualified for the intent-to-treat anal., and 24 completed 12 mo of treatment. Repeated-measures anal. of variance within subjects showed significant improvements in Clin. Global Impressions severity and improvement, Modified Symptom Checklist, and Quality of Life Questionnaire scores. One patient developed a rash that was judged to be a serious drug-related side effect. The most common side effects were headache (n=25), nausea (n=21), insomnia (n=18), dry mouth (n=18), and sweating

(n=18). The results demonstrate the safety and patient acceptance of venlafaxine in depressed geriatric outpatients for acute and maintenance treatment.

IT **93413-69-5**, Venlafaxine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(venlafaxine in depressed human geriatric outpatients)

L3 ANSWER 602 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:225263 CAPLUS
DN 124:278742
TI The neuroendocrine effects of venlafaxine in healthy subjects
AU Daffner-Bugia, C.; Laakmann, G.; Voderholzer, U.; Haag, C.; Baghai, T.; Kolmsee, S.; Schroeder, U.; Munz, T.
CS Psychiatric Hospital, University Munich, Munich, D-80336, Germany
SO Human Psychopharmacology (1996), 11(1), 1-9
CODEN: HUPSEC; ISSN: 0885-6222
PB Wiley
DT Journal
LA English
AB Venlafaxine-HCl represents a novel chemical class of antidepressants. In preclin. studies it had monoamine uptake inhibitory properties. It specifically inhibited the uptake of serotonin (5-HT) norepinephrine (NE) and dopamine (DA) in rat brain synaptosomes. Previous studies showed that various classes of psychotropic drugs with different effects on central aminergic systems exhibit distinct neuroendocrine profiles. In this study, the authors investigated the effect of ascending doses of venlafaxine (12.5 mg, 25 mg, 50 mg, 75 mg orally) on neuroendocrine function in 6 healthy male subjects, using a single-blind, placebo-controlled study design. After the ascending doses of venlafaxine, an effect on GH, and prolactin after the higher doses of venlafaxine was demonstrated. The cortisol secretion was statistically significantly influenced by venlafaxine, and showed a dose dependent increase. These neuroendocrine effects of venlafaxine may be interpreted as being a result of 5-HT and NE reuptake-inhibition properties of the substance. Evidence for a DA reuptake-inhibition was not found as DA-agonists lead to an inhibition of prolactin secretion.

IT **93413-69-5**, Venlafaxine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(neuroendocrine effects of venlafaxine in humans)

L3 ANSWER 603 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:224280 CAPLUS
DN 124:306555
TI Pharmacokinetic interaction between multiple-dose venlafaxine and single-dose lithium
AU Troy, Steven M.; Parker, Vernon D.; Hicks, David R.; Boudino, F. Douglas; Chiang, Soong T.
CS Clinical Research and Development, Wyeth-Ayerst Research, Philadelphia, PA, 19101-1245, USA
SO Journal of Clinical Pharmacology (1996), 36(2), 175-81
CODEN: JCPCBR; ISSN: 0091-2700
PB Lippincott-Raven
DT Journal
LA English
AB An open-label study was conducted to evaluate the effects of multiple-dose, steady-state venlafaxine administration on the pharmacokinetics of a single oral dose of Li+ in healthy men. Analogously, the effects of administration of a single dose of Li+ on the disposition of venlafaxine and its active metabolite, O-

demethylvenlafaxine, after multiple-dose administration of venlafaxine were assessed. Administration of 600 mg Li2CO3 did not affect venlafaxine absorption. Li+ reduced the renal clearance of venlafaxine from 0.053 to 0.027 L/h/kg. However, renal excretion is not a major elimination pathway for venlafaxine; thus, Li+ did not affect the total clearance of venlafaxine. Li+ administration had similar effects on elimination of O-demethylvenlafaxine. Multiple-dose administration of 50 mg venlafaxine every 8 h produced a slight increase in the rate of Li+ absorption, but did not affect the extent of Li+ absorption. Total clearance (0.026 L/h/kg) and steady-state volume of distribution (0.71 L/kg) of Li+ were not affected by administration of venlafaxine. Thus, there were no clin. significant pharmacokinetic interactions between venlafaxine and Li+.

IT 554-13-2, Lithium carbonate 7439-93-2, Lithium, biological studies **93413-69-5**, Venlafaxine
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pharmacokinetic interaction between multiple-dose venlafaxine and single-dose lithium in humans)

L3 ANSWER 604 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:167258 CAPLUS
DN 124:278711
TI Venlafaxine oxidation in vitro is catalyzed by CYP2D6
AU Otton, S. V.; Ball, S. E.; Cheung, S. W.; Inaba, T.; Rudolph, R. L.; Sellers, E. M.
CS Clinical Research and Treatment Institute, Addiction Research Foundation, Toronto, ON, M5S 2S1, Can.
SO British Journal of Clinical Pharmacology (1996), 41(2), 149-56
CODEN: BCPHBM; ISSN: 0306-5251
PB Blackwell
DT Journal
LA English
AB Several selective 5-HT reuptake inhibitors (SSRIs) are inhibitors of the genetically polymorphic drug metabolizing enzyme, CYP2D6. We studied the interaction of venlafaxine, a new SSRI, with CYP2D6 in human liver microsomes. Venlafaxine was a less potent inhibitor of this enzyme activity in vitro than other SSRIs tested. The average apparent Ki values determined using CYP2D6-dependent dextromethorphan O-demethylation were: 33, 52 and 22 μM for rac-venlafaxine, R(+)-venlafaxine and S(-)-venlafaxine resp., vs 0.065 to 1.8 μM for paroxetine, fluoxetine, norfluoxetine, fluvoxamine and sertraline. Microsomes from human livers (n=3) and from yeast transformed with an expression plasmid containing human CYP2D6 cDNA catalyzed the O-demethylation of venlafaxine, which is the major metabolic pathway in vivo. Intrinsic metabolic clearance values (Vmax/Km) indicated that S(-)-venlafaxine was cleared preferentially via this pathway. In microsomes from CYPD6-deficient livers (n=2), Vmax/Km of O-demethylation of venlafaxine was one to two orders of magnitude lower and was similar to the rate of N-demethylation. Studies with chemical probes which preferentially inhibit P 450 isoforms suggested that CYP3A3/4 is involved in venlafaxine N-demethylation. These in vitro findings predict phenotypic differences in the kinetics of venlafaxine in vivo, although the clin. importance of this is unclear as O-demethylvenlafaxine is pharmacol. similar to the parent drug. The findings also predict relatively limited pharmacokinetic interaction between venlafaxine and other CYP2D6 substrates.

IT 93413-45-7, S-(-)-Venlafaxine hydrochloride 93413-47-9, R-(+)-Venlafaxine hydrochloride **93413-69-5**, Venlafaxine
RL: RCT (Reactant); RACT (Reactant or reagent)
(venlafaxine oxidation in vitro is catalyzed by cytochrome P 450 CYP2D6)

L3 ANSWER 605 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN

10/290,245

AN 1996:113382 CAPLUS
DN 124:156011
TI Potentiation of drug response by a serotonin 1A receptor antagonist
IN Wong, David Taiwai; Oguiza, Juan Ignacio
PA Eli Lilly and Co., USA
SO Eur. Pat. Appl., 24 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 687472	A2	19951220	EP 1994-307876	19941026
	EP 687472	A3	19970115		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	CA 2134038	AA	19951217	CA 1994-2134038	19941021
	CA 2134038	C	19970603		
	NO 9404046	A	19951218	NO 1994-4046	19941024
	HU 71582	A2	19951228	HU 1994-3071	19941024
	AU 9477421	A1	19960104	AU 1994-77421	19941024
	AU 685510	B2	19980122		
	ZA 9408357	A	19960424	ZA 1994-8357	19941024
	SG 70562	A1	20000222	SG 1996-8007	19941026
	CN 1113436	A	19951220	CN 1994-119338	19941027
	JP 08003035	A2	19960109	JP 1994-284933	19941118
	US 5532268	A	19960702	US 1995-442735	19950517
	US 5532244	A	19960702	US 1995-442737	19950517
	US 5538992	A	19960723	US 1995-442734	19950517
	US 5552429	A	19960903	US 1995-442733	19950517
PRAI	US 1994-260857	A	19940616		
	US 1994-277460	A	19940719		

OS MARPAT 124:156011
AB The power of serotonin and norepinephrine reuptake inhibitors, such as fluxetine, venlafaxine, milnacipran and duloxetine to increase the availability of serotonin, norepinephrine and dopamine, particularly serotonin, is augmented by administration in combination with a drug which is a serotonin 1A receptor antagonist. A capsule contained fluoxetine.HCl 20, pindolol 30, starch 200, and Mg stearate 10 mg.
IT 54910-89-3D, Fluoxetine, mixture with serotonin 1A receptor antagonists
92623-85-3D, Milnacipran, mixture with serotonin 1A receptor antagonists
93413-69-5D, Venlafaxine, mixture with serotonin 1A receptor antagonists 116539-59-4D, Duloxetine, mixture with serotonin 1A receptor antagonists 173478-21-2 173478-22-3 173478-23-4 173478-24-5 173478-25-6 173478-26-7
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(potentiation of drug response by a serotonin 1A receptor antagonist)

L3 ANSWER 606 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1996:4521 CAPLUS
DN 124:135413
TI Venlafaxine: Measuring the onset of antidepressant action
AU Derivan, Albert; Entsuah, A. Richard; Kikta, Dianne
CS Wyeth-Ayerst Research, Clinical Research and Development, Philadelphia, PA, 19101-8299, USA
SO Psychopharmacology Bulletin (1995), 31(2), 439-47
CODEN: PSYBB9; ISSN: 0048-5764
PB U.S. Dep. of Health and Human Services
DT Journal
LA English
AB Venlafaxine, a new antidepressant, inhibits reuptake of norepinephrine and

serotonin without appreciable effects on histaminergic, α-adrenergic, or cholinergic systems. Pharmacol. the drug is unique:. The half life is short and it exerts both rapid and prolonged β-adrenergic desensitization after single doses in a rodent model. Venlafaxine has been thought to possess a rapid onset of clin. antidepressant action. Accordingly, two clin. studies in which moderate amts. of venlafaxine were given aggressively were reviewed to examine aspects of the drug's onset of action. Three statistical methodologies were employed-traditional anal. of depression scale scores, pattern anal. based on timing and persistence of response, and survival anal. of sustained response. All three methods showed venlafaxine to have significant effects early in the course of therapy. In addition, venlafaxine is the first drug to meet criteria for early onset using the pattern anal. methodol. Depressed patients aggressively treated with venlafaxine show significant benefit on or before Day 7 of treatment using traditional methods of anal. as well as survival anal. of sustained response.

IT **93413-69-5**, Venlafaxine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(venlafaxine and measuring the onset of antidepressant action)

L3 ANSWER 607 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:892012 CAPLUS
DN 123:275917
TI Presynaptic Ca2+/calmodulin-dependent protein kinase II: autophosphorylation and activity increase in the hippocampus after long-term blockade of serotonin reuptake
AU Popoli, Maurizio; Vocaturo, Claudia; Perez, Jorge; Smeraldi, Enrico; Racagni, Giorgio
CS Inst. Pharmacol. Sci., Univ. Milan, Milan, Italy
SO Molecular Pharmacology (1995), 48(4), 623-9
CODEN: MOPMA3; ISSN: 0026-895X
PB Williams & Wilkins
DT Journal
LA English
AB It is known that long-term treatment with antidepressants induces an enhancement of neurotransmission in the pathway projecting from raphe nuclei to the hippocampus. In the case of selective serotonin (5-HT) reuptake inhibitors, this enhancement is due to a desensitization of presynaptic 5-HT autoreceptors and a concomitant increase in 5-HT release in terminal areas. To investigate whether this effect is accompanied by adaptive changes in the mol. machinery regulating transmitter release at serotonergic terminals, autophosphorylation and activity of Ca2+/calmodulin-dependent protein kinase II were measured in subsynaptosomal fractions from hippocampus and total cortex. Long-term treatment with 2 selective serotonin reuptake inhibitors (paroxetine and fluvoxamine) and with a nonselective reuptake inhibitor (venlafaxine) induces a large increase of kinase autophosphorylation in synaptic vesicles and synaptic cytosol in the hippocampus but not in synaptosomal membranes. No significant change was detected in total cortex. The change is not reproduced by the direct addition of the drugs to the phosphorylation system and is not elicited by acute treatment of the animals. The increase in autophosphorylation is not accounted for by neosynthesis or translocation of the kinase to synaptic terminals. The change is restricted to the kinase located inside the terminals and is not detected in synaptosomal membranes, containing predominantly postsynaptic kinase, suggesting that only presynaptic kinase is affected. In the same fractions, the kinase activity is increased. These results are in agreement with reports suggesting a presynaptic effect for the SSRIs and disclose a new putative site of action for psychotropic drugs.
IT 54739-18-3, Fluvoxamine **93413-69-5**, Venlafaxine

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(presynaptic Ca2+/calmodulin-dependent protein kinase II: autophosphorylation and activity increase in hippocampus after long-term blockade of serotonin reuptake)

L3 ANSWER 608 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:792829 CAPLUS
DN 123:188626
TI Venlafaxine and its analogs for inducing cognition enhancement
IN Husbands, George Edward Morris; Abou-Gharbia, Magid Abdel-Megid; Moyer, John Allen; Muth, Eric Anthony
PA American Home Products Corp., USA
SO Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 667150	A1	19950816	EP 1995-300612	19950131
	EP 667150	B1	20021211		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	EP 1245228	A2	20021002	EP 2002-14620	19950131
	EP 1245228	A3	20021009		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
	AT 229328	E	20021215	AT 1995-300612	19950131
	PT 667150	T	20030228	PT 1995-95300612	19950131
	ES 2185683	T3	20030501	ES 1995-300612	19950131
	CA 2141774	AA	19950815	CA 1995-2141774	19950203
	JP 07252143	A2	19951003	JP 1995-23837	19950213
PRAI	US 1994-195417	A	19940214		
	EP 1995-300612	A3	19950131		

OS MARPAT 123:188626
AB This invention provides use of a compound to manufacture a medicament of inducing
cognition enhancement. The compound is a 2-(1-hydroxycycloalkyl or 1-hydroxycycloalkenyl)-2-phenylalkylamine derivative, preferably venlafaxine (I) and its pharmaceutically acceptable salts. I was subjected to the scopolamine-impaired radial arm maze tests with rats. I produced a significant decrease in scopolamine impairment with ED50 value of 1mg/kg i.p.
IT **93413-69-5**, Venlafaxine 99300-78-4, Venlafaxine hydrochloride
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(venlafaxine and its analogs for inducing cognition enhancement)

L3 ANSWER 609 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:750272 CAPLUS
DN 123:159908
TI Selective serotonin/noradrenaline reuptake inhibitors (SNRIs). Pharmacology and therapeutic potential in the treatment of depressive disorders
AU Artigas, Francesc
CS Dep. Neurochem., Consejo Super. Invest. Cientificas, Barcelona, Spain
SO CNS Drugs (1995), 4(2), 79-89
CODEN: CNDREF; ISSN: 1172-7047
PB Adis
DT Journal; General Review
LA English
AB A review, with 71 refs., of the structure, disposition, and pharmacol. actions of the antidepressant SNRIs duloxetine, milnacipran and

venlafaxine.

IT 92623-85-3, Milnacipran **93413-69-5**, Venlafaxine 116539-59-4, Duloxetine
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antidepressant pharmacol. of)

L3 ANSWER 610 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:652583 CAPLUS
DN 123:25692
TI Use of hydroxycycloalkanephenethylamines as antidepressant and antiobesity agents
IN Rudolph, Richard L.; Derivan, Albert T.; Muth, Eric A.; Upton, Gertrude V.
PA American Home Products Corp., USA
SO Can. Pat. Appl., 13 pp.
CODEN: CPXXEB
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	CA 2126305	AA	19941229	CA 1994-2126305	19940620
	EP 639374	A2	19950222	EP 1994-304252	19940613
	EP 639374	A3	19950802		
	EP 639374	B1	20020220		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	EP 1153603	A2	20011114	EP 2001-115854	19940613
	EP 1153603	A3	20030521		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
	AT 213407	E	20020315	AT 1994-304252	19940613
	ES 2174864	T3	20021116	ES 1994-304252	19940613
	JP 07089851	A2	19950404	JP 1994-137282	19940620
	AU 9465929	A1	19950105	AU 1994-65929	19940623
	US 5916923	A	19990629	US 1997-835780	19970408
	AU 9858312	A1	19980521	AU 1998-58312	19980310
	US 6310101	B1	20011030	US 1999-285812	19990402
	AU 744990	B2	20020307	AU 2000-53350	20000814
	US 2001012855	A1	20010809	US 2001-769998	20010125
	US 6444708	B2	20020903		
	US 2001053799	A1	20011220	US 2001-892363	20010627
	US 6465524	B2	20021015		
	US 2002052405	A1	20020502	US 2001-996590	20011130
	US 6555586	B2	20030429		
	LV 12881	B	20021120	LV 2002-152	20020815
	US 2003181517	A1	20030925	US 2003-396043	20030325
PRAI	US 1993-83848	A	19930628		
	EP 1994-304252	A3	19940613		
	US 1995-368521	B1	19950104		
	US 1997-835780	A3	19970408		
	US 1999-285812	A3	19990402		
	AU 2000-43783	A3	20000630		
	US 2001-769998	A3	20010125		
	US 2001-892363	A3	20010627		
	US 2001-996590	A3	20011130		

OS MARPAT 123:25692
AB Hydroxycycloalkanephenethylamines are useful for treatment of obesity, generalized anxiety disorder, post-traumatic stress disorder, late luteal phase dysphoric disorder (premenstrual syndrome), attention deficit disorder, with and without hyperactivity, Gilles de la Tourette syndrome, bulimia nervosa of and Shy Drager Syndrome (Markush structure given). Venlafaxine was administered orally at 25-225 mg/day to 18-65 yr old

patients. The mean decrease in body weight after 10 wk was 3.6%.
IT **93413-69-5**, Venlafaxine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cycloalkanephenethylamines as antidepressant and antiobesity agents)

L3 ANSWER 611 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:630192 CAPLUS
DN 123:40949
TI Pharmaceutical compositions containing venlafaxine or aryloxy propanamine derivatives for treatment of incontinence
IN Thor, Karl Bruce
PA Eli Lilly and Co., USA
SO Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 654264	A1	19950524	EP 1994-308604	19941122
	EP 654264	B1	20010530		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	CA 2136120	AA	19950525	CA 1994-2136120	19941118
	ZA 9409190	A	19960520	ZA 1994-9190	19941118
	NO 9404456	A	19950526	NO 1994-4456	19941121
	IL 111705	A1	20010111	IL 1994-111705	19941121
	AU 9478968	A1	19950601	AU 1994-78968	19941122
	AU 679269	B2	19970626		
	JP 07188003	A2	19950725	JP 1994-288119	19941122
	ES 2157958	T3	20010901	ES 1994-308604	19941122
	PT 654264	T	20010928	PT 1994-94308604	19941122
	CN 1107699	A	19950906	CN 1994-118993	19941123
	CN 1099284	B	20030122		
	HU 72317	A2	19960429	HU 1994-3369	19941123
	HU 218920	B	20001228		
	RU 2152786	C2	20000720	RU 1994-41950	19941123
	CZ 289069	B6	20011017	CZ 1994-2893	19941123
	US 5744474	A	19980428	US 1995-425703	19950420
	HK 1013799	A1	20020208	HK 1998-115196	19981223
	CZ 290573	B6	20020814	CZ 2001-1091	20010323
PRAI	US 1993-158121	A	19931124		
	CZ 1994-2893	A3	19941123		

OS MARPAT 123:40949
AB Urinary incontinence in humans is treated by administration of venlafaxine or a compound chosen from a series of aryloxy propanamines (Markush structure given). Thus, 13.5 g of (S)-(-)-N,N-dimethyl-3-hydroxy-3-(2-ethienyl)propanamine (preparation given) in dimethylsulfoxide was reacted with 12.8 g 1-fluoronaphthalene and stirred for 2.5 h at 60-65° to obtain (S)-(+)-N,N-dimethyl-3-(naphthalenyloxy)-3-(2-ethienyl)propanamine (I). I was dissolved in 14% EtOH (10mg/mL) and diluted with saline to allow appropriate dose injection in a volume of 0.1-0.3 mL/kg i.v. to cats. I produced dose-dependent increase in bladder capacity, to about 5 times the capacity seen under control conditions. A capsule contained I.HCl 5, starch 445, and Mg stearate 10 mg.
IT **93413-69-5P**, Venlafaxine 116817-77-7P 132335-44-5P 136434-34-9P 164015-33-2P 164015-34-3P 164015-36-5P 164015-37-6P 164015-38-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(pharmaceutical compns. containing venlafaxine or aryloxy propanamine derivs. for treatment of incontinence)

L3 ANSWER 612 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:574861 CAPLUS
DN 123:301
TI Pharmacokinetic and pharmacodynamic evaluation of the potential drug interaction between venlafaxine and diazepam
AU Troy, Steven M.; Lucki, Irwin; Peirgies, Antoni A.; Parker, Vernon D.; Klockowski, Patricia M.; Chiang, Soong T.
CS Wyeth-Ayerst Research, Philadelphia, PA, 19101, USA
SO Journal of Clinical Pharmacology (1995), 35(4), 410-19
CODEN: JCPCBR; ISSN: 0091-2700
DT Journal
LA English
AB To assess possible pharmacokinetic and pharmacodynamic interactions between the antidepressant venlafaxine and diazepam, a randomized, two-period, crossover study was conducted in 18 men. Multiple-dose venlafaxine (50 mg every 8 h) or placebo (double-blind) was given for 10 days; on day 4 a single placebo dose (same appearance as diazepam capsule, single-blind) was given; and on day 5 a single dose of diazepam (10 mg) was given. Pharmacokinetic data indicated that diazepam had no significant effect on venlafaxine or O-desmethylvenlafaxine disposition. Diazepam pharmacokinetics were minimally changed in the presence of venlafaxine. Diazepam oral clearance (CL/f) increased slightly (24 ± 8 vs. 26 ± 6 mL/h/kg; P = .007), volume of distribution (Vz/f) increased (0.85 ± 0.28 vs. 0.99 ± 0.34 L/kg; P = .02), and AUC decreased (5973 ± 2304 vs. 5008 ± 1354 ng·h/mL; P = .02). Venlafaxine did not alter desmethyldiazepam pharmacokinetics. Pharmacodynamic data showed a statistically significant diazepam-venlafaxine interaction for only one of the eight psychometric tests given. Critical flicker fusion slightly decreased (P = .01) between placebo-diazepam (37.85 ± 3.28 Hz) and venlafaxine-diazepam (37.09 ± 4.13 Hz) treatments. The observed pharmacokinetic and pharmacodynamic interactions between diazepam and venlafaxine were small and probably clin. insignificant.
IT 439-14-5, Diazepam **93413-69-5**, Venlafaxine
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmacokinetic and pharmacodynamic drug interaction between venlafaxine and diazepam)

L3 ANSWER 613 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:574860 CAPLUS
DN 123:173
TI The pharmacokinetics of venlafaxine when given in a twice-daily regimen
AU Troy, Steven M.; Parker, Vernon D.; Fruncillo, Richard J.; Chiang, Soong T.
CS Wyeth-Ayerst Research, Philadelphia, Philadelphia, PA, 19101, USA
SO Journal of Clinical Pharmacology (1995), 35(4), 404-9
CODEN: JCPCBR; ISSN: 0091-2700
DT Journal
LA English
AB The comparative bioavailability of the novel antidepressant venlafaxine and its pharmacol. active metabolite O-desmethylvenlafaxine was assessed when venlafaxine was given orally twice daily (75 mg bid) or 3 times daily (50 mg tid). Eighteen healthy subjects participated in an open-label, randomized, two-period, crossover study lasting 12 days. Each subject was randomly assigned to take venlafaxine according to a bid or a tid regimen through day 8 and was crossed over to the other regimen on days 9 to 12. The daily dose was titrated up to 150 mg/d and was held constant on days 5 to 12. Plasma samples for quantitation of venlafaxine and O-desmethylvenlafaxine were obtained during a 24-h steady-state interval

on days 8 and 12. Anal. of variance showed no significant differences between the two venlafaxine regimens for peak concentration (Cmax), area under the curve during 24 h (AUC0-24), trough concentration, or fluctuation ratio for venlafaxine or O-desmethylvenlafaxine in plasma. The bioequivalence ratios for Cmax and AUC0-24 of both compds. were calculated to compare the bid regimen and the tid regimen. The mean value for each of the 4 ratios was between 96 and 100%, and the 90% confidence limits around each ratio were within 90 to 110%. These results indicate that dividing a daily 150-mg venlafaxine dose into 2 or 3 doses provides equivalent total exposure and peak plasma concns. of venlafaxine and O-desmethylvenlafaxine, its active metabolite. Therefore, based on pharmacokinetic considerations, it appears that the same daily dose of venlafaxine can be given in either two or three divided doses without compromising efficacy.

IT 93413-62-8, O-Desmethylvenlafaxine **93413-69-5**, Venlafaxine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pharmacokinetics of venlafaxine given in twice-daily regimen in humans)

L3 ANSWER 614 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:424176 CAPLUS
DN 122:177504
TI Venlafaxine: a review of its pharmacology and therapeutic potential in depression
AU Holliday, Stephen M.; Benfield, Paul
CS Adis International Limited, Auckland, N. Z.
SO Drugs (1995), 49(2), 280-94
CODEN: DRUGAY; ISSN: 0012-6667
DT Journal; General Review
LA English
AB A review with 61 refs. Venlafaxine is a phenylethylamine derivative which facilitates neurotransmission in the brain by blocking presynaptic reuptake of serotonin (5-hydroxytryptamine; 5-HT) and noradrenaline (norepinephrine). Clin. data from patients with major depression are consistent with the favorable efficacy and tolerability profile of venlafaxine predicted by pharmacodynamic studies. In patients with major depression, venlafaxine 75 to 375 mg/day administered for 6 wk was significantly more effective than placebo, and at least as effective as imipramine, clomipramine, trazodone or fluoxetine. Venlafaxine is well tolerated, being associated with fewer anticholinergic and CNS adverse effects than tricyclic antidepressants. Unlike the tricyclic antidepressants, venlafaxine does not appear to significantly affect cardiac conduction, although there have been a few reports of modest increases in blood pressure, particularly after high doses of the drug. In conclusion, wider clin. experience is required to better characterize and confirm potential advantages of venlafaxine compared with other antidepressant agents. These advantages may include a rapid onset of action and reduced propensity to cause anticholinergic effects and cardiotoxicity compared with tricyclic antidepressants. Nevertheless, at this stage venlafaxine offers a more attractive treatment option than tricyclic antidepressants for patients with major depression, primarily because of its good overall tolerability profile.

IT **93413-69-5**, Venlafaxine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(venlafaxine pharmacol. and its therapeutic potential in depression)

L3 ANSWER 615 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1995:324843 CAPLUS
DN 122:89459
TI Antidepressant dosage forms comprising dialkylaminoethane derivatives
IN Edgren, David E.; Bhatti, Gurdish Kaur; Hatamkhani, Zahedeh; Wong, Patrick S.-L.

10/290,245

PA Alza Corp., USA
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9427589	A2	19941208	WO 1994-US6049	19940527
	WO 9427589	A3	19950126		
	W: AU, CA, FI, JP, KR, NO, NZ				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, NL, PT, SE				
	US 6440457	B1	20020827	US 1993-68480	19930527
	CA 2157186	AA	19941208	CA 1994-2157186	19940507
	AU 9470482	A1	19941220	AU 1994-70482	19940527
	AU 677080	B2	19970410		
	ZA 9403743	A	19950124	ZA 1994-3743	19940527
	EP 700289	A1	19960313	EP 1994-919286	19940527
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	JP 08510755	T2	19961112	JP 1994-501005	19940527
	NO 9504694	A	19951124	NO 1995-4694	19951121
	FI 9505681	A	19951124	FI 1995-5681	19951124
PRAI	US 1993-68480	A	19930527		
	WO 1994-US6049	W	19940527		

OS MARPAT 122:89459
AB Controlled-release tablets contain antidepressant dialkylaminoethane derivs. (Markush structure given) for an extended period of time in a rate-known dose. A controlled-release tablet was prepared which released in stimulated intestinal fluid 77 mg venlafaxine.HCl at a zero-order rate over an extended duration of 16 h.
IT **93413-69-5**, Venlafaxine 99300-78-4, Venlafaxine hydrochloride
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antidepressant dosage forms comprising dialkylaminoethane derivs.)

L3 ANSWER 616 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:449972 CAPLUS
DN 121:49972
TI Binding of antidepressants to human brain receptors: focus on newer generation compounds
AU Cusack, Bernadette; Nelson, Albert; Richelson, Elliott
CS Dep. Res., Mayo Clin. Jacksonville, Jacksonville, FL, 32224, USA
SO Psychopharmacology (Berlin, Germany) (1994), 114(4), 559-65
CODEN: PSCHDL; ISSN: 0033-3158
DT Journal
LA English
AB Using radioligand binding assays and post-mortem normal human brain tissue, the authors obtained equilibrium dissociation consts. (Kds) for 17 antidepressants and two of their metabolites at histamine H1, muscarinic, α1-adrenergic, α2-adrenergic, dopamine D2, serotonin 5-HT1A, and serotonin 5-HT2 receptors. Several newer antidepressants were compared with older drugs. In addition, the authors studied some antimuscarinic, antiparkinson, antihistamine, and neuroleptic compds. at some of these receptors. For the antidepressants, classical tricyclic antidepressants were the most potent drugs at five of the seven receptors (all but α2-adrenergic and 5-HT1A receptors). The chlorophenylpiperazine derivative antidepressants (etoperidone, nefazodone, trazodone) were the most potent antidepressants at α2-adrenergic and 5-HT1A receptors. Of ten antihistamines tested, none was more potent than doxepin at histamine H1 receptors. At muscarinic receptors antidepressants and antihistamines had a range of potencies, which were mostly weaker than those for antimuscarinics. From the in vitro data, the authors expect adinazolam, bupropion, fluoxetine, sertraline, tomoxetine,

and venlafaxine not to block any of these five receptors in vivo. An antidepressant's potency for blocking a specific receptor is predictive of certain side effects and drug-drug interactions. These studies can provide guidelines for the clinician in the choice of antidepressant.

IT 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 51-55-8, Atropine, biological studies 58-73-1, Diphenhydramine 59-33-6 60-87-7, Promethazine 68-88-2, Hydroxyzine 72-69-5, Nortriptyline 77-37-2, Procyclidine 83-98-7, Orphenadrine 113-59-7, Chlorprothixene 129-03-3, Cyproheptadine 132-17-2 144-11-6, Trihexyphenidyl 486-12-4, Triprolidine 514-65-8, Biperiden 768-94-5, Amantadine 1668-19-5, Doxepin 2062-78-4, Pimozide 6581-06-2, QNB 19794-93-5, Trazodone 23047-25-8, Lofepramine 25523-97-1, d-Chlorpheniramine 28797-61-7, Pirenzepine 29216-28-2, Mequitazine 34911-55-2, Bupropion 36505-84-7, Buspirone 37115-32-5, Adinazolam 50679-08-8, Terfenadine 52942-31-1, Etoperidone 54910-89-3, Fluoxetine 59859-58-4, Femoxetine 61869-08-7, Paroxetine 79617-96-2, Sertraline 83015-26-3, Tomoxetine 83366-66-9, Nefazodone 83891-03-6, Norfluoxetine 87857-41-8, Desmethylsertraline **93413-69-5**, Venlafaxine 102394-31-0, AF-DX 116
RL: PROC (Process)
(binding of, to human brain receptors)

L3 ANSWER 617 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:400192 CAPLUS
DN 121:192
TI Pharmacokinetics of venlafaxine and O-desmethylvenlafaxine in laboratory animals
AU Howell, S. R.; Hicks, D. R.; Scatina, J. A.; Sisenwine, S. F.
CS Drug Metab. Div., Wyeth-Ayerst Res., Princeton, NJ, 08543-8000, USA
SO Xenobiotica (1994), 24(4), 315-27
CODEN: XENOBH; ISSN: 0049-8254
DT Journal
LA English
AB The pharmacokinetics of venlafaxine has been evaluated in mouse, rat, dog, and rhesus monkey after i.v. and/or i.g. doses of venlafaxine from 2 to 120 mg/kg either as single or repeated doses. In rat, dog, and monkey, venlafaxine is a high clearance compound with a large volume of distribution after i.v. administration. Absolute bioavailability was low in rat and rhesus monkey (12.6 and 6.5%, resp.) and moderate in dog (59.8%). Other species differences were seen, including an elimination half-life of venlafaxine that was longer in dog and rhesus monkey (2-4 h) than in rodent (around 1 h). In mouse, rat, and dog, exposure to venlafaxine increased more than proportionally with dose, suggesting saturation of elimination. Exposure of venlafaxine decreased with repeated dosing in mouse and rat, but was unchanged in dog. Exposure of animals to the bioactive metabolite, O-desmethylvenlafaxine (ODV), was less than that of venlafaxine itself. ODV was not detected in dog and not measurable in rhesus monkey receiving venlafaxine.
IT **93413-69-5**, Venlafaxine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pharmacokinetics of, species differences in relation to)

L3 ANSWER 618 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:400117 CAPLUS
DN 121:117
TI A high-performance liquid chromatographic method for the simultaneous determination of venlafaxine and O-desmethylvenlafaxine in biological fluids
AU Hicks, David R.; Wolaniuk, Donna; Russell, Anita; Cavanaugh, Nancy; Kraml, Michael
CS Drug Metab. Div., Wyeth-Ayerst Res., Princeton, NJ, USA

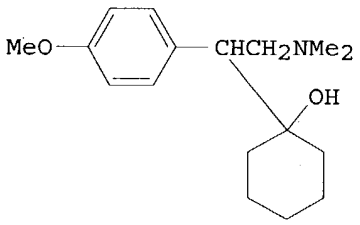
10/290,245

SO Therapeutic Drug Monitoring (1994), 16(1), 100-7
CODEN: TDMODV; ISSN: 0163-4356
DT Journal
LA English
AB A rapid, accurate, and sensitive high-performance liquid chromatog. (HPLC) method for simultaneous determination of venlafaxine (V) and O-desmethylvenlafaxine (ODV) in plasma and urine has been developed. V and ODV are extracted from plasma using a liquid-liquid extraction procedure, chromatographed on a Supelcosil LC-8DB column, and quantitated by UV detection at 229 nm. Linearity was established over the range 10-500 ng/mL for V and 7.2-720 ng/mL for ODV using 1.0 mL of human, rat, dog, and mouse plasma. For urine, for both analytes, an anal. range 0.1-10.0 μg/mL was established. Accuracy of > ±10% about the theor. mean was achieved for all matrixes, with intra- and interday coeffs. of variation for precision of <10%. Endogenous components in plasma and/or urine or known metabolites of V do not interfere in the determination of the analytes. For both V and ODV, a quantitation limit of 10 ng/mL for plasma was adequate for their estimation over a period of three half-lives, following administration of a pharmacol. dose in man, and the limit of 0.1 μg/mL, for urine, can monitor excretion of as little as 0.5% of the dose.
IT **93413-69-5**, Venlafaxine
RL: ANT (Analyte); ANST (Analytical study)
(determination of, in blood and urine of humans and laboratory animals by HPLC)

L3 ANSWER 619 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1994:45707 CAPLUS
DN 120:45707
TI Venlafaxine exhibits pre-clinical antidepressant activity in the resident-intruder social interaction paradigm
AU Mitchell, Paul J.; Fletcher, Allan
CS Neuropharmacol. Group, Wyeth Res. (UK) Ltd., Taplow/Maidenhead/Berkshire, SL6 0PH, UK
SO Neuropharmacology (1993), 32(10), 1001-9
CODEN: NEPHBW; ISSN: 0028-3908
DT Journal
LA English
AB Venlafaxine, a novel 2-phenyl-2-(1-hydroxycycloalkyl) ethylamine (I), is a potent inhibitor of 5-hydroxytryptamine and noradrenaline reuptake and exhibits a profile of activity in pre-clin. in vitro biochem. studies predictive of antidepressant activity. The studies described here examined the effects of acute and chronic treatment with I on the behavior of resident rats confronted with an unfamiliar, non-treated, intruder conspecific. Ethol. anal. of the social encounters revealed that acute, s.c., treatment with I, 20-180 μmol kg-1, induced a selective, dose-related, reduction in aggressive behavior (ID50 = 24.87 μmol kg-1) concomitant with increased flight behavior. In contrast, chronic treatment with I, 20 μmol kg-1 day-1, via s.c.-implanted osmotic mini-pumps, induced a marked elevation in aggressive behavior concomitant with reduced flight behavior. These diametrically opposite effects of acute and chronic I treatment on the agonistic behavior of resident rats are consistent with the behavioral effects of similar treatment regimes previously identified for a range of antidepressant drugs that differ widely in their acute pharmacol. These data strongly support the potential antidepressant activity of I and are consistent with the results of recent clin. trials which demonstrate that I exhibits significant antidepressant activity.
IT **93413-69-5**, Venlafaxine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antidepressant activity of, social and agonist behavior response to)

L3 ANSWER 620 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:595047 CAPLUS
DN 119:195047
TI Metabolic disposition of 14C-venlafaxine in mouse, rat, dog, rhesus monkey and man
AU Howell, S. R.; Husbands, G. E. M.; Scatina, J. A.; Sisenwine, S. F.
CS Drug Metab. Div., Wyeth-Ayerst Res., Princeton, NJ, 08543-8000, USA
SO Xenobiotica (1993), 23(4), 349-59
CODEN: XENOBH; ISSN: 0049-8254
DT Journal
LA English
GI



I

AB The metabolic disposition of venlafaxine (I) has been studied in mouse, rat, dog, rhesus monkey and man after oral doses (22, 22, 2, and 10 mg/kg, and 50 mg, resp.) of 14C-venlafaxine as the hydrochloride. In all species, over 85% of the administered radioactivity was recovered in the urine within 72 h, indicating extensive absorption from the GI tract and renal excretion. Venlafaxine was extensively metabolized, with only 13.0, 1.8, 7.9, 0.3 and 4.7% dose appearing as parent compound in urine of mouse, rat, dog, monkey and man, resp. The metabolite profile varied significantly among species, but primary metabolic reactions were demethylations and the conjugation of phase I metabolites. Hydroxylation of the cyclohexyl ring also occurred in mouse, rat and monkey, and a cyclic product was formed in rat and monkey. Glucuronidation was the primary conjugation reaction, although sulfate conjugates were also detected in mouse urine. While no metabolite constituted more than 20% dose in any species except man, the major urinary metabolites were: mouse, N,O-didesmethylvenlafaxine glucuronide; rat, cis-1,4-dihydroxyvenlafaxine; dog, O-desmethylvenlafaxine glucuronide; monkey, N,N,O-tridesmethylvenlafaxine; and man, O-desmethylvenlafaxine.
IT **93413-69-5**, Venlafaxine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, in humans and laboratory animals)

L3 ANSWER 621 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:531407 CAPLUS
DN 119:131407
TI Antagonism of the five cloned human muscarinic cholinergic receptors expressed in CHO-K1 cells by antidepressants and antihistaminics
AU Stanton, Tiffany; Bolden-Watson, Carolyn; Cusack, Bernadette; Richelson, Elliott
CS Dep. Psychiatry, Mayo Found. and Mayo Clin., Jacksonville, FL, 32224, USA
SO Biochemical Pharmacology (1993), 45(11), 2352-4
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English

10/290,245

AB Based on mol. cloning studies, five different muscarinic receptor subtypes exist: m1, m2, m3, m4, and m5. The authors determined the affinity and selectivity of binding for sixteen antidepressants, two of their metabolites, and three antihistaminics (H1) at these subtypes. Using Chinese hamster ovary cells (CHO-K1) transfected with genes for the human muscarinic receptor subtypes, the authors obtained equilibrium dissociation consts.
(Kds) from competitive radioligand binding studies with [3H]-quinuclidinyl benzilate ([3H]QNB) and membrane prepns. of these cells. QNB was the most potent compound studied (Kd 30-80 pM). Mequitazine (Kd 6-14 nM) and amitriptyline (Kd 7-16 nM) exhibited the highest affinity among the antihistaminics and antidepressants, resp. Among the antidepressants examined were the serotonin-selective drugs sertaline and fluoxetine, both of which displayed Kd values >1 μM. The remaining antidepressants were moderate to weak antagonists with some eliciting no radioligand competition at high concns. The compds. studied showed no significant selectivity among the five cloned subtypes.

IT 50-47-5, Desipramine 50-48-6, Amitriptyline 50-49-7, Imipramine 72-69-5, Nortriptyline 83-98-7, Orphenadrine 113-53-1, Dothiepin 129-03-3, Cyproheptadine 1668-19-5, Doxepin 6581-06-2, QNB 19794-93-5, Trazodone 23047-25-8, Lofepramine 29216-28-2, Mequitazine 34911-55-2, Bupropion 37115-32-5, Adinazolam 52942-31-1, Etoperidone 54910-89-3, Fluoxetine 59859-58-4, Femoxetine 61869-08-7, Paroxetine 79617-96-2, Sertraline 83891-03-6, Norfluoxetine 87857-41-8, Desmethylsertraline **93413-69-5**, Venlafaxine
RL: PROC (Process)
(binding of, to human muscarinic receptor subtypes, expressed in Chinese hamster ovary cells)

L3 ANSWER 622 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1993:183305 CAPLUS
DN 118:183305
TI Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes
AU Bolden-Watson, C.; Richelson, E.
CS Mayo Clin., Jacksonville, FL, 32224, USA
SO Life Sciences (1993), 52(12), 1023-9
CODEN: LIFSAK; ISSN: 0024-3205
DT Journal
LA English
AB We determined the uptake blockade produced by eight new antidepressant drugs (etoperidone, femoxetine, lofepramine, nefazodone, paroxetine, sertraline, tomoxetine, and venlafaxine), two metabolites of newer antidepressants, and carbamazepine. Inhibitor consts. (Kis) for uptake blockade were obtained from competitive uptake studies with [3H]norepinephrine, [3H]5-hydroxytryptamine, and [3H]dopamine in rat brain synaptosomes prepared from hippocampus, frontal cortex, and striatum, resp. Among the newer compds., tomoxetine (Ki = 0.7 nM) and lofepramine (Ki = 1.9 nM) were potent and selective]3H]norepinephrine uptake blockers; paroxetine (Ki = 0.73 nM), sertraline (Ki = 3.4 nM), and femoxetine (Ki = 22 nM) potently and selectively inhibited [3H]5-hydroxytryptamine uptake. Although none of the drugs was potent for [3H]dopamine uptake blockade, sertraline was the most potent (Ki = 260 nM). These data are useful in predicting adverse effects and drug-drug interactions of antidepressants.

IT 50-47-5, Desipramine 50-48-6 50-49-7, Imipramine 72-69-5, Nortriptyline 113-53-1, Dothiepin 298-46-4, Carbamazepine 1668-19-5, Doxepin 19794-93-5, Trazodone 23047-25-8, Lofepramine 34911-55-2, Bupropion 52942-31-1, Etoperidone 54910-89-3, Fluoxetine 59859-58-4, Femoxetine 61869-08-7, Paroxetine 79617-96-2, Sertraline 83015-26-3, Tomoxetine 83366-66-9, Nefazodone 83891-03-6, Norfluoxetine 87857-41-8, Desmethylsertraline **93413-69-5**, Venlafaxine
RL: BIOL (Biological study)

(biogenic amine uptake inhibition by, in brain synaptosomes, antidepressant activity in relation to)

L3 ANSWER 623 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:482830 CAPLUS
DN 117:82830
TI The disposition of venlafaxine enantiomers in dogs, rats, and humans receiving venlafaxine
AU Wang, C. Paul; Howell, Stanley R.; Scatina, Joann; Sisenwine, Samuel F.
CS Drug Metab. Div., Wyeth-Ayerst Res., Princeton, NJ, 08543, USA
SO Chirality (1992), 4(2), 84-90
CODEN: CHRLEP; ISSN: 0899-0042
DT Journal
LA English
AB A stereospecific HPLC method was developed for the quantitation of the enantiomers of venlafaxine, an antidepressant, in dog, rat, and human blood plasma. The procedure involves derivatization of venlafaxine with the chiral reagent, (+)-S-naproxen chloride, and a post-derivatization procedure. The method was linear in the range of 50-5000 ng of each enantiomer per mL of plasma. No interference by endogenous substances or known metabolites of venlafaxine occurred. Studies to characterize the disposition of the enantiomers of venlafaxine were conducted in the dog, rat, and human, following oral administration of venlafaxine. The Cmax, area under the curve (AUC) and (S)/(R) concentration ratios of the (R)- and (S)-enantiomers were compared. In rats, the mean plasma ratio of (S)-venlafaxine to (R)-venlafaxine over 0.5-6.0 h varied from 2.97 to 8.50 with a mean value of 5.51. The Cmax, AUC0-∞, and t1/2 values of the (R)- and (S)-enantiomers in dogs were not different from one another. The mean (S)/(R) ratios mean of enantiomers of venlafaxine in human over a 2-6 h interval ranged from 1.33 to 1.35 with an overall ratio of 1.34. These ratios were not different from unity, indicating that the disposition of venlafaxine enantiomers in humans is not stereoselective and is more similar to that in dogs than that in rats.
IT 93413-44-6 93413-46-8 **93413-69-5**, (±)-Venlafaxine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pharmacokinetics of, stereoselectivity of, HPLC assay in relation to, in humans and laboratory animals)

L3 ANSWER 624 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:462857 CAPLUS
DN 117:62857
TI Pharmacodynamics of venlafaxine evaluated by EEG brain mapping, psychometry and psychophysiology
AU Saletu, B.; Gruenberger, J.; Anderer, P.; Linzmayer, L.; Semlitsch, H. V.; Magni, G.
CS Sch. Med., Univ. Vienna, Vienna, A-1090, Austria
SO British Journal of Clinical Pharmacology (1992), 33(6), 589-601
CODEN: BCPHBM; ISSN: 0306-5251
DT Journal
LA English
AB In a double-blind, placebo-controlled study the effects of venlafaxine - a novel nontricyclic compound inhibiting neuronal uptake of serotonin, noradrenaline and to a lesser extent dopamine - were investigated by using EEG brain mapping, psychometric and psychophysiol. measures. Sixteen healthy volunteers received randomized and at weekly intervals single oral doses of placebo, 12.5 mg, 25 mg, and 50 mg of venlafaxine. EEGS recordings, psychometric and psychophysiol. tests, and evaluation of pulse, blood pressure and side-effects were carried out at 0, 2, 4, 6, and 8 h. EEG brain mapping demonstrated that venlafaxine exerted a significant action on human brain function as compared with placebo at all three doses, characterized mostly by attenuation of absolute power, increase

of relative delta/theta and beta, and decrease of alpha power, as well as by an acceleration of the total centroid fronto-temporally and by its slowing centrally and parietally. These findings are similar to antidepressants such as imipramine. Topog., drug-induced alterations were most pronounced over both fronto-temporal and the right temporal to temporo-occipital regions. Psychometric and psychophysiol. investigations demonstrated significant dose-dependent psychotropic properties of the drug. Multivariate statistics exhibited an improvement of both the noopsyche (e.g. attention, concentration variability, memory, fine motor activity, reaction time performance) and thymopsyche (e.g. drive, wakefulness)) but also significant psychophysiol. activation (e.g. in c.f.f., pupillary and skin conductance measures). Time-efficiency calcns. showed significant central effects from the 2nd hour onwards, with increasing differences between placebo and treatment up to the 8th hour. Nausea was the most frequent complaint and appeared dose-dependent.

IT **93413-69-5**, Venlafaxine
RL: BIOL (Biological study)
(pharmacodynamics of, in humans)

L3 ANSWER 625 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1992:120776 CAPLUS
DN 116:120776
TI Evaluation of the discriminative stimulus effects of venlafaxine, a potential antidepressant, in rhesus monkeys
AU Nader, Michael A.; Woolverton, William L.
CS Drug Abuse Res. Cent., Univ. Chicago, Chicago, IL, 60637, USA
SO Drug Development Research (1992), 25(1), 75-80
CODEN: DDREDK; ISSN: 0272-4391
DT Journal
LA English
AB The discriminative stimulus effects of the novel antidepressant venlafaxine were examined in rhesus monkeys. Sep. groups of monkeys discriminated either 0.56 or 1.0 mg/kg (i.g.) d-amphetamine (N = 3) or 10 mg/kg (i.g.) pentobarbital (N = 4) from saline, in a discrete-trials shock avoidance/escape paradigm. In d-amphetamine-trained monkeys, 10-17 mg/kg venlafaxine occasioned only saline-appropriate responding and had minimal effect on response latency in all monkeys. The highest dose of venlafaxine tested (30 mg/kg) occasioned at least 95% d-amphetamine-lever responding in two of three monkeys. Following this dose, the average latency to respond after the onset of a trial increased substantially in both monkeys; in one monkey avoidance responding was disrupted and shocks were occasionally received. In the third monkey, 30 mg/kg venlafaxine occasioned only saline-lever responding and had no effect on response latency. In pentobarbital-trained monkeys, venlafaxine (3.0-30 mg/kg) occasioned primarily saline-lever responding and these doses had minimal effects on response latency. In general, venlafaxine was more potent in d-amphetamine-trained monkeys than in pentobarbital-trained monkeys in its effects on response latency. Drug discrimination procedures in animals have been shown to differentiate compds. in a manner that is consistent with their subjective effects. Thus, results from the present experiment suggest that venlafaxine may produce subjective effects similar to d-amphetamine in some individuals, but only at high doses.

IT **93413-69-5**, Venlafaxine
RL: PRP (Properties)
(discriminative stimulus effect of)

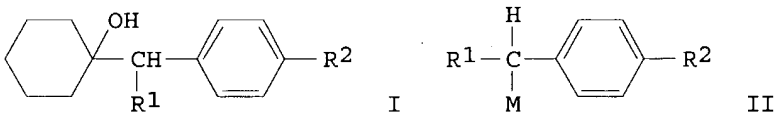
L3 ANSWER 626 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1991:485257 CAPLUS
DN 115:85257
TI Biochemical, neurophysiological, and behavioral effects of Wy-45,233 and other identified metabolites of the antidepressant venlafaxine
AU Muth, Eric A.; Moyer, John A.; Haskins, J. Thomas; Andree, Terrance H.;

Husbands, G. E. Morris
CS Wyeth-Ayerst Res., Princeton, NJ, 08543-8000, USA
SO Drug Development Research (1991), 23(2), 191-9
CODEN: DDREDK; ISSN: 0272-4391
DT Journal
LA English
AB Seven metabolites of venlafaxine, identified in several species, were examined for central pharmacol. activity in rodents. The O-desmethyl compound Wy-45,233, which is the major metabolite in man, had the greatest preclin. activity. This metabolite exhibited an antidepressant profile (monoamine uptake blockade, reversal of reserpine hypothermia, induction of pineal β-adrenergic subsensitivity) comparable to the parent drug, venlafaxine. This compound also inhibited serotonergic and noradrenergic firing rates like the parent compound, but with less potency. The cyclohexyl ring-hydroxylated metabolite Wy-47,877 and the N-desmethylmetabolite Wy-45,494 were also active in reserpine hypothermia, but Wy-45,494 was a weaker inhibitor of serotonin uptake and both metabolites were weaker inhibitors of norepinephrine uptake than Wy-45,233. None of the 7 metabolites tested exhibited significant binding at dopamine-2, muscarinic cholinergic, α-1-adrenergic, histamine-1, or opiate (μ) receptors. These results suggest that Wy-45,233, the O-desmethyl metabolite of venlafaxine, is an active metabolite which retains the benign side-effect profile of venlafaxine.
IT **93413-69-5**, Venlafaxine
RL: PRP (Properties)
(behavioral and biochem. and neurophysiol. effects of, anticonvulsion in relation to)

L3 ANSWER 627 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1991:81228 CAPLUS
DN 114:81228
TI Preparation of cyclohexanol derivatives as intermediates for antidepressants
IN Shepherd, Robin Gerald
PA John Wyeth and Brother Ltd., UK
SO Brit. UK Pat. Appl., 15 pp.
CODEN: BAXXDU
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	GB 2227743	A1	19900808	GB 1990-2095	19900130
	GB 2227743	B2	19920617		
	US 5043466	A	19910827	US 1990-471187	19900126
PRAI	GB 1989-2209		19890201		

OS CASREACT 114:81228; MARPAT 114:81228
GI



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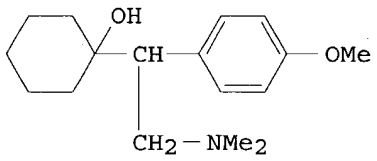
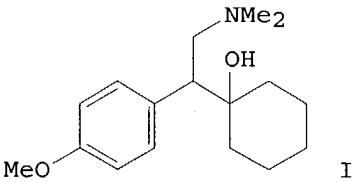


III

AB Title compds. I [R1 = cyano, CONMe2, CSNMe2; R2 = OMe, (protected) OH], useful as intermediates for preparation of antidepressants, were prepared by reaction of II [M = Li, Na, K, or MgX (X = halo); R2 = OMe, protected OH] with cyclohexanone in hydrocarbon/ether solvents. For example, II (R1 = CSNMe2, R2 = OMe, M = MgBr) gave the corresponding I in 64% yield. Subsequent reduction of I by Raney-Ni gave the antidepressant (no data) N,N-dimethyl-2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)ethylamine (III).

IT 93413-62-8P **93413-69-5P** 99300-78-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as antidepressant)

L3 ANSWER 628 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:630878 CAPLUS
DN 113:230878
TI 2-Phenyl-2-(1-hydroxycycloalkyl)ethylamine derivatives: synthesis and antidepressant activity
AU Yardley, John P.; Husbands, G. E. Morris; Stack, Gary; Butch, Jacqueline; Bicksler, James; Moyer, John A.; Muth, Eric A.; Andree, Terrance; Fletcher, Horace, III; et al.
CS Wyeth-Ayerst Res., Princeton, NJ, 08543-8000, USA
SO Journal of Medicinal Chemistry (1990), 33(10), 2899-905
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CASREACT 113:230878
GI



I

AB A series of 2-phenyl-1-(1-hydroxycycloalkyl)ethylamine derivs. was examined for the ability to inhibit both rat brain imipramine receptor binding and the synaptosomal uptake of norepinephrine (NE) and serotonin (5-HT). Neurotransmitter uptake inhibition was highest for a subset of 2-phenyl-2-(1-hydroxycyclohexyl)dimethylethylamines in which the aryl ring has a halogen or methoxy substituent at the 3- and/or 4-positions. Potential antidepressant activity in this subset was assayed in three

rodent models-the antagonism of reserpine-induced hypothermia, the antagonism of histamine-induced ACTH release, and the ability to reduce noradrenergic responsiveness in the rat pineal gland. An acute effect seen in the rat pineal gland with several analogs, including 1-[1-(3,4-dichlorophenyl)-2-(dimethylamino)ethyl]cyclohexanol and 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol (I), was taken as a possible correlate of a rapid onset of antidepressant activity. Compound I (venlafaxine) is presently undergoing clin. evaluation.

IT 93413-38-8P 93413-39-9P 93413-40-2P 93413-41-3P 93413-44-6P
93413-45-7P 93413-46-8P 93413-47-9P 93413-48-0P 93413-50-4P
93413-51-5P 93413-62-8P 93413-65-1P **93413-69-5P**
93413-71-9P 93413-72-0P 93413-73-1P 93413-74-2P 93413-75-3P
93413-77-5P 93413-82-2P 93413-86-6P 93413-89-9P 93413-90-2P
93413-92-4P 93413-93-5P 93413-94-6P 93413-95-7P 93413-96-8P
93413-99-1P 93414-00-7P 93414-01-8P 93414-02-9P 93414-03-0P
93414-04-1P 99300-78-4P 130198-05-9P 130198-15-1P 130198-17-3P
130198-22-0P 130198-27-5P 130198-28-6P 130198-29-7P 130198-30-0P
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130198-43-5P 130198-44-6P 130198-45-7P 130198-46-8P 130198-47-9P
130198-48-0P 130198-49-1P 130198-52-6P 130198-53-7P 130198-55-9P
130198-57-1P 130198-58-2P 130198-59-3P 130198-61-7P 130198-62-8P
130198-63-9P 130198-64-0P 142733-20-8P 149289-30-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and antidepressant activity of)

L3 ANSWER 629 OF 629 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1985:5895 CAPLUS
DN 102:5895
TI Phenethylamine derivatives and intermediates
IN Husbands, George Edward Morris; Yardley, John Patrick; Muth, Eric Anthony
PA American Home Products Corp., USA
SO Eur. Pat. Appl., 58 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 112669	A2	19840704	EP 1983-307435	19831207
	EP 112669	A3	19841128		
	EP 112669	B1	19870729		
	R: AT, BE, CH, DE, FR, IT, LI, LU, NL, SE				
	US 4535186	A	19850813	US 1983-545701	19831026
	CA 1248540	A1	19890110	CA 1983-441289	19831116
	AU 8322123	A1	19840621	AU 1983-22123	19831206
	AU 567524	B2	19871126		
	ZA 8309073	A	19840926	ZA 1983-9073	19831206
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	GB 2133788	B2	19870715		
	AT 28628	E	19870815	AT 1983-307435	19831207
	FI 8304523	A	19840614	FI 1983-4523	19831209
	FI 77647	B	19881230		
	FI 77647	C	19890410		
	DK 8305713	A	19840614	DK 1983-5713	19831212
	DK 166372	B	19930419		
	DK 166372	C	19930906		
	HU 33097	O	19841029	HU 1983-4231	19831212
	HU 199104	B	19900129		
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	GB 2173787	B2	19870715		
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	JP 03178953	A2	19910802	JP 1990-267501	19901003
	JP 05030826	B4	19930511		
PRAI	US 1982-449032		19821213		
	US 1983-486594		19830419		
	GB 1983-16646		19830618		
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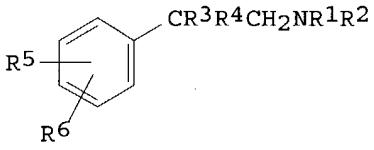
	GB 1983-32598		19831207		

OS CASREACT 102:5895

GI



I

AB About 35 I [R1 = H, C1-6 alkyl; R2 = C1-6 alkyl; R3 = optionally unsatd. 1-hydroxycycloalkyl, optionally unsatd. 1-alkoxycycloalkyl, 1-cycloalkenyl; R4 = H, C1-6 alkyl; R5, R6 = H, OH, C1-6 alkyl, alkoxy, alkanoyloxy, -CN, NO2, alkylthio, NH2, alkylamino, dialkylamino, carboxamido, halo, CF3; R5R6 = methylenedioxy], antidepressants, were prepared E.g., p-MeOC6H4CH2CN in THF was treated with BuLi at -70°, then condensed with cyclohexanone at -50° to give 1-[cyano(p-methoxyphenyl)methyl]cyclohexanol (II). II was hydrogenated in NH3-EtOH over 5% Rh on Al2O3, then methylated with HCHO and HCO2H to give 1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol (III). III showed an activity equal to imipramine in synaptosomal NE and 5-HT uptake inhibition. Also, unlike the tricyclic antidepressants, III and related compds. demonstrate neither muscarinic anticholinergic activity nor antihistaminic activities.

IT 93413-56-0P **93413-69-5P** 93413-70-8P 93413-71-9P
93413-72-0P 93413-73-1P 93413-74-2P 93413-75-3P 93413-89-9P
93413-92-4P 93413-93-5P 93413-94-6P 93413-96-8P 99300-78-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and antidepressant activity of)

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